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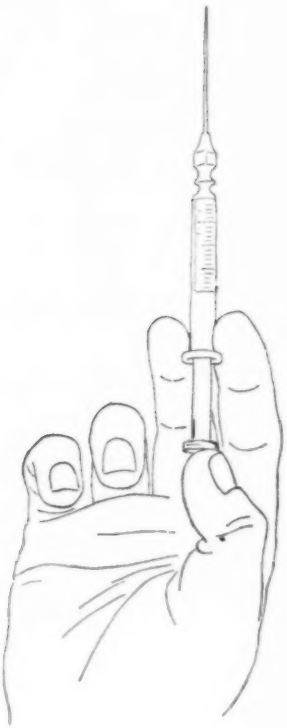

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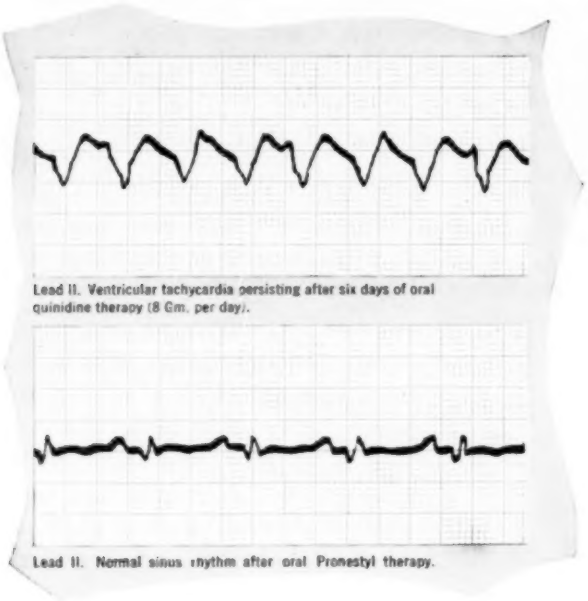

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VOLUME 62 *December 1950* NUMBER 6

THREE-YEAR FOLLOW-UP STUDY ON 202 CASES OF PULMONARY TUBERCULOSIS TREATED WITH STREPTOMYCIN[1,2]

ROBERT O. CANADA, STANTON T. ALLISON, NICHOLAS D. D'ESOPO, EDWARD DUNNER, RALPH E. MOYER, ARNOLD SHAMASKIN, CARL W. TEMPEL, AND WILBUR V. CHARTER

(Received for publication April 25, 1950)

INTRODUCTION

The cooperative project of the Veterans Administration, Army, and Navy, designed to study the effect of streptomycin upon human tuberculosis, was one of the first large-scale investigations of its kind. Protocols were carefully planned to ensure uniformity of material and procedure in the various study units. Treatment of the initial group of patients was begun in July 1946, and during the following nine months 223 patients with pulmonary tuberculosis were treated in the seven Federal hospitals participating in the study. The immediate results of therapy were reported in the December 1947 issue of THE AMERICAN REVIEW OF TUBERCULOSIS. The present report is based on a follow-up survey of 202 of these patients which was made approximately three years after streptomycin therapy was completed.

Clinical Series and Plan of Study

The follow-up survey was accomplished by an investigator from each of the original study units. Where possible, patients who had been discharged from the hospital were readmitted for the follow-up studies. Where this was not possible, the patients were examined in an outpatient status in a Federal hospital or a regional office of the Veterans Administration. A standard form was used for recording data obtained from the follow-up studies. By these means, information, partial or complete, was obtained for 202 of the original 223 patients. The original hospital records were carefully reviewed so that the clinical observations made at the beginning and end of the streptomycin therapy might be compared with the clinical observations made at the time of the follow-up study.

The majority of the tuberculous patients in these Federal hospitals during 1946 were young men from the armed forces whose disease had become evident during or immedi-

[1] Presented before the Medical Session, as part of the symposium on *Chemotherapy*, at the 46th annual meeting of the National Tuberculosis Association, Washington, D. C., April 25, 1950.

[2] The opinions and assertions contained herein are the private ones of the authors and are not to be construed as official or as reflecting the views of the Veterans Administration or Departments of the Army or Navy.

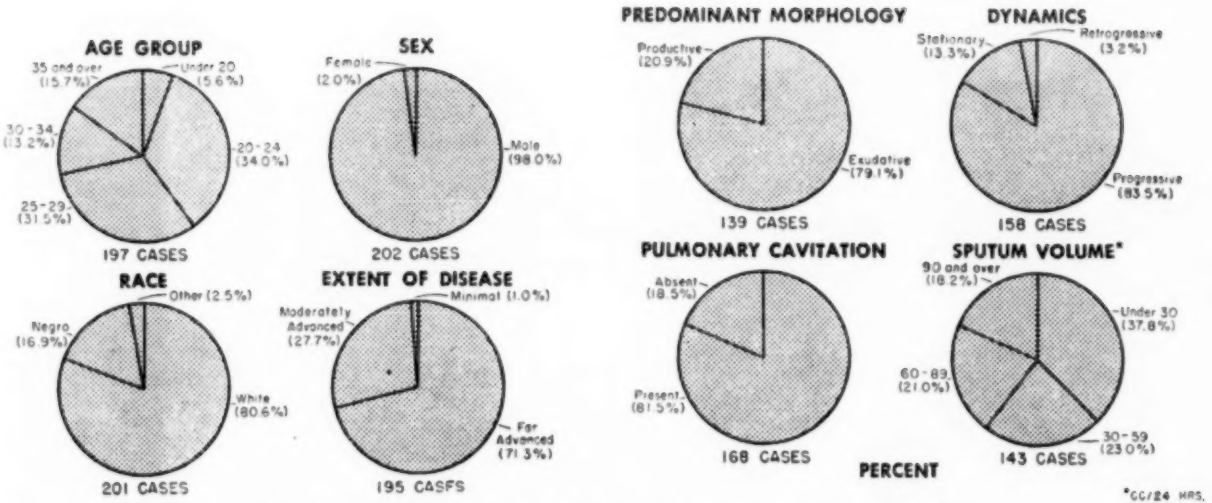

FIG. 1. Clinical material and status of disease at beginning of streptomycin therapy

ately following World War II. One of the major objectives of the study was to observe the effect of streptomycin upon the acute tuberculous lesion. Stipulations in the protocol required that the tuberculous lesion have an exudative component, and that the disease be progressive or at least stationary during a minimum pretreatment observation of sixty days. Thus, the type of patient chosen for treatment was one not likely to show spontaneous remission. The patients who most readily fulfilled these requirements were those with bronchopneumonic disease or advanced cavernous disease with acute bronchogenic dissemination, a group whose prognosis was poor. The type of patient treated is represented in figure 1. The term exudative, as used in this report, refers to those abnormal shadows from the lung parenchyma which appear "soft" and have poorly defined borders. Productive refers to those abnormal shadows with fairly well-defined borders. The latter characteristic undoubtedly permits inclusion of fibrotic as well as proliferative lesions, and both classifications include caseous disease. The dynamics of the disease was judged by comparison of roentgenograms taken approximately two months prior to therapy with those taken within a few days of the date streptomycin therapy was be-

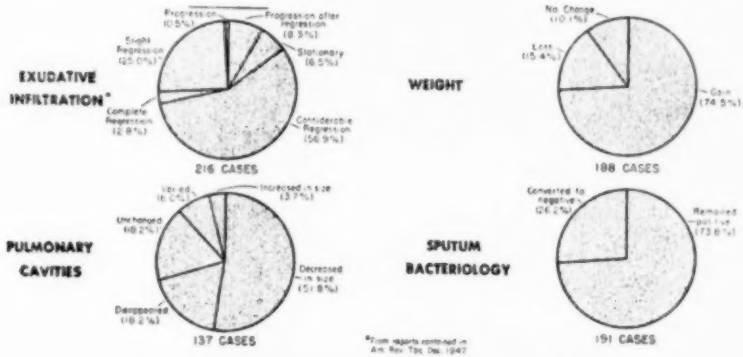

FIG. 2. Changes observed during streptomycin therapy

gun. In general, this group of patients may be described as young adult males with progressive, predominantly exudative, advanced pulmonary tuberculosis.

OBSERVATIONS DURING THERAPY

Streptomycin was administered in total daily dosage of 1.8 or 2 gm. for a period of 120 days. Concomitant with streptomycin therapy, symptomatic and roentgenographic improvement occurred at a rate and to a degree hitherto not seen in this type of tuberculosis. These changes are depicted in figure 2 and are given in more detail in previous reports (1–7). Although improvement was dramatic in some patients, it was often short-lived. Roentgenographic evidence of relapse was observed in 24 per cent of the patients toward the end of therapy and during the first four months following therapy.

OBSERVATIONS SUBSEQUENT TO THERAPY

In the present study an effort has been made to determine the factors which influenced the status of the patients three years after therapy. As shown in table 1, 56 patients were dead at time of follow-up and all but 2 of these patients died

as a result of tuberculosis. In 56 other patients, the disease remained active or quiescent, and in 75 the disease had become arrested or apparently arrested. Of the living patients, 35 per cent were employed in gainful occupations and an additional 15 per cent were able to be up and about nine or more hours a day. Twenty-four per cent of the living patients had remained continuously under hospital treatment since completion of streptomycin therapy.

Mortality: The mortality for the entire group during the three-year period following streptomycin therapy was 28 per cent. Of the variables studied, age, race, and extent of disease at the beginning of therapy were factors which seemed to affect the survival of the patients.

The mortality in patients under 25 years of age was 35 per cent, compared with 23 per cent for the group 25 years of age and older. The majority of deaths in the group of younger patients occurred in the first year subsequent to therapy,

TABLE 1

Patients with Specified Activity of Disease Three Years after Streptomycin Therapy Classified by Age at Beginning of Therapy

AGE AT BEGINNING OF THERAPY	TOTAL PATIENTS	DEAD PATIENTS	PATIENTS LIVING THREE YEARS AFTER THERAPY				
			Active	Quiescent	Apparently arrested	Arrested	Activity not reported
All ages	202	56	40	16	11	64	15
Under 20 years	11	6	—	—	1	3	1
20 to 24 years	67	21	10	4	2	24	6
25 to 29 years	62	7	15	6	5	26	3
30 to 34 years	26	8	6	4	2	6	—
35 years and over	31	12	8	1	1	5	4
Age not reported	5	2	1	1	—	—	1

whereas in the older group only 33 per cent of deaths occurred during that period. The group of patients under 25 years of age was comparable to the group 25 years and older in the prevalence of advanced lesions, progressive lesions, and pulmonary cavitation as observed at the beginning of therapy. Likewise, there was no significant difference between the two groups in the number or type of collapse measures initiated following streptomycin therapy. There was, however, a higher proportion of predominantly exudative lesions in the younger group (90 per cent compared with 73 per cent).

There were 39 nonwhite patients, or 19 per cent of the total; of these, all except 5 were Negro. The fatality rate in the nonwhite races was 41 per cent, compared to 25 per cent in the white race. The two groups were comparable in the number of advanced lesions, progressive lesions, and pulmonary cavitation. The nonwhite patients were younger than the white patients, however; 59 per cent of the former, and only 39 per cent of the latter being less than 25 years of age. More of the nonwhite patients had predominantly exudative lesions at the start of therapy (91 per cent compared with 76 per cent in the white patients).

The mortality rate in patients who had far advanced disease at the beginning of therapy (36 per cent) was almost three times as great as in patients who had minimal or moderately advanced disease (13 per cent). As a corollary to this, only one death occurred in 31 patients whose roentgenograms taken at the start of therapy failed to show pulmonary cavitation.

Arrested and apparently arrested cases: As shown in table 1, 75, or 40 per cent, of the patients attained arrest or apparent arrest of their disease during the three-year period following streptomycin therapy. Again the age of the patient and the extent of the disease at the start of therapy were related to the disease activity found at time of the follow-up. Although the fatality rate was higher in those patients under 25 years of age, the disease became inactive more often in members of the younger group who were still living three years after therapy (68 per cent compared with 53 per cent in the older group). Patients

TABLE 2

Patients with Specified Roentgenographic Changes in Chest as a Whole, Classified by Time Period*

TIME PERIOD	PATIENTS* WITH SPECIFIED DEGREE OF CHANGE						
	Improvement			No change	Worsening		
	Marked	Moderate	Slight		Slight	Moderate	Marked
Start of streptomycin therapy to present	72	14	5	3	2	5	—
End of streptomycin therapy to present†	28	35	18	7	1	10	2

* Based on 101 patients.

† Three-year interval.

judged to have minimal or moderately advanced disease at the start of therapy attained arrest or apparent arrest of their disease almost twice as often as did those with far advanced disease (60 per cent compared with 33 per cent). When only the living patients were considered, the prevalence of inactive disease in the minimal-moderately advanced group was still significantly higher (70 per cent) than in the far advanced group (52 per cent). Neither the pretreatment dynamics nor the morphology of the lesion was of any significance when related to the activity of the disease process observed three years after therapy.

Changes in the chest roentgenogram: Roentgenograms taken at the beginning and at the end of streptomycin therapy were compared with those taken approximately three years later in 101 patients now living. The changes which occurred during the two periods were graded according to degree of improvement or worsening. The results are recorded in table 2. Inclusion of the four-month treatment period made a considerable difference in the degree of improvement observed. Marked improvement was noted almost three times as often during the interval from the beginning of therapy until the present as was noted in the same patients from the end of therapy until the present. The post-therapy films

showed a decrease in the degree of improvement and an increase in the degree of deterioration.

Bacteriologic examination of sputum (table 3)*:* Four patients had sputum negative for tubercle bacilli at the time streptomycin therapy was started. Discounting these 4 patients, sputum conversion occurred during therapy in 46 of 187 patients (25 per cent). During the years following treatment, an additional 25 per cent converted to negative. Of 50 patients with sputum negative for tubercle bacilli at completion of therapy, 7 became positive and 5 others died during the period since therapy.

Following streptomycin therapy, collapse measures were used in 91 patients, or two-thirds of the total number of patients for whom information was available. Sputum conversion occurred in 60 per cent of the patients who received collapse.

TABLE 3

Patients with Specified Sputum Status Three Years after Streptomycin Therapy, Classified by Sputum Status at End of Therapy*

SPUTUM STATUS AT END OF STREPTOMYCIN THERAPY	TOTAL PATIENTS	DEAD PATIENTS	PATIENTS WITH SPECIFIED SPUTUM STATUS THREE YEARS AFTER THERAPY		
			Positive	Negative	Sputum status not reported
Total	202	56	35	80	31
Positive sputum	141	48	25	48	20
Negative sputum	50	5	7	29	9
Sputum status not reported	11	3	3	3	2

* Smear or culture of sputum or culture of gastric washings.

Streptomycin resistance: Data were collected on 247 streptomycin sensitivity tests made on bacteria obtained from 80 patients during the three-year period which has elapsed since streptomycin was first initiated. Table 4 shows the results of these tests according to the months that have elapsed since the beginning of streptomycin therapy. In this table only one test per patient was included for a single period. When more than one test had been made in a given period, the result showing the highest degree of resistance was used. After the third month of therapy, approximately 20 per cent of the tests indicated that the strains were sensitive to less than 10 γ of streptomycin per cc. This level of sensitivity was maintained through the third year following streptomycin therapy. No patients showed a sustained decrease in resistance. Re-treatment with streptomycin may have played a part in maintaining resistance in 5 of 18 cases resistant twenty-four or more months after beginning the initial course of therapy.

Toxic residua: Vertigo or ataxia, or both, were present in 81 per cent of the patients at some time during therapy. These two conditions were most often observed together. Only 7 patients had vertigo without ataxia, and 4 had ataxia

without vertigo. Of 100 patients who had vertigo during treatment and on whom data were available three years after therapy, the symptoms had disappeared in 57 but remained in some degree in 43 patients. Of 99 patients who had ataxia during therapy, the symptoms had disappeared in 51 and remained in some degree in 48. In no patient had vertigo or ataxia become worse. Response to caloric stimulation was impaired or absent in 88 of 113 patients at the end of therapy, and it remained so in 41 of 95 patients given the test three years after therapy. There was return of vestibular function to normal, as determined by the caloric test, in one-third of the patients listed as having total loss of function at the end of streptomycin therapy. In 8 of 122 patients for whom the question was answered, it was considered that vestibular dysfunction at the time of the follow-up would interfere with a gainful occupation.

TABLE 4

Number and Percentage of Patients Whose Cultures Were Found to Have Resistance to Streptomycin, Classified by Interval from Beginning of Treatment*

Interval from beginning of treatment	Cultures exhibiting growth in specified ranges of streptomycin concentration						
	Total†	Less than 10 γ per cc.		10 to 99 γ per cc.		100 γ per cc. or more	
		Number	Per cent of total	Number	Per cent of total	Number	Per cent of total
Before treatment	43	40	93	3	7	—	—
Less than 2 months	29	27	92	1	4	1	4
2 to 3 months	50	15	30	16	32	19	38
4 to 5 months	34	7	21	8	23	19	56
6 to 11 months	29	6	21	12	41	11	38
12 to 23 months	39	7	18	11	28	21	54
24 months or more	23	5	22	5	22	13	56

* Reported as the lowest concentration of streptomycin by which growth was inhibited.

† Based on 247 cultures of *M. tuberculosis* obtained from 80 patients; only one test per patient was included for each time period.

Of 115 patients living three years after therapy, it was recorded that 9 had experienced impaired hearing during streptomycin therapy. Seven of the 9 still had impaired hearing, and in 3 the condition had become worse.

SUMMARY

1. This report summarizes a survey made approximately three years after therapy of 202 patients with pulmonary tuberculosis treated with streptomycin in dosage of 1.8 to 2.0 gm. per day for 120 days. A majority of the patients had progressive, predominantly exudative, advanced pulmonary tuberculosis at the time streptomycin therapy was initiated.

2. During the three-year period following streptomycin therapy, 28 per cent of 202 patients died. Arrest or apparent arrest of the disease was attained in 40 per cent of 187 patients for whom this information was available. In 30 per

cent of this number, the disease remained active or quiescent. Approximately one-third of the living patients were gainfully employed and one-half were able to be up and about nine or more hours per day.

3. The mortality rate was highest in the nonwhite races and in patients less than 25 years of age. Although the mortality rate was higher and death occurred earlier in the patients under 25 years of age, those who survived the three-year post-treatment period more often presented inactive disease than did those 25 years and older.

4. Sputum conversion occurred in 25 per cent of the patients during therapy and in an additional 25 per cent during the period since therapy. Seven of 29 patients negative at the end of therapy and living three years later had reconverted to positive.

5. Multiple streptomycin sensitivity tests performed on tubercle bacilli obtained from 80 patients after the completion of 120 days of streptomycin therapy demonstrated organisms resistant to more than 10 γ of streptomycin per cc. in 80 per cent of the cases. There was no indication of decrease in the incidence or degree of resistance during the three years following therapy.

6. Approximately one-half of the patients who exhibited vestibular disturbance during therapy still had residuals of this three years later. In none was the condition worse than at the end of therapy. It was the opinion of the examining physicians that in 6 per cent of the living patients the severity of the residual vertigo or ataxia was sufficient to interfere with gainful occupation.

SUMARIO

Estudio Trienal de 202 Casos de Tuberculosis Pulmonar Tratados con Estreptomicina

1. Este estudio, ejecutado unos tres años después de la terapéutica, comprende la observación subsiguiente de 202 tuberculosos pulmonares tratados con estreptomicina a dosis de 1.8 a 2.0 gm. diarils durante 120 días. La mayoría de los enfermos tenían tuberculosis pulmonar avanzada, evolutiva, predominantemente exudativa al iniciar la estreptomicinoterapia.

2. Durante el trienio consecutivo a la estreptomicinoterapia, falleció un 28 por ciento de los 202 pacientes. Obtúvose estacionamiento real o aparente de la enfermedad en 40 por ciento de los 187 enfermos para los cuales se contaba con esta información; y en 30 por ciento de los mismos la enfermedad continuaba en forma activa o quiescente. Aproximadamente la tercera parte de los sujetos vivos estaban empleados lucrativamente y la mitad podían estar levantados nueve o más horas al día.

3. El índice de mortalidad alcanzó su máximo en las razas no blancas y en los enfermos de menos de 25 años de edad. Aunque dicho índice fué más alto y la muerte sobrevino más pronto en los enfermos de menos de 25 años, los que sobrevivieron el trienio de posttratamiento presentaron enfermedad inactiva más a menudo que los de 25 años o más.

4. Hubo viraje del esputo en 25 por ciento durante la terapéutica y en otro 25

por ciento más en el período subsiguiente. Siete de 29 enfermos negativos al terminar el tratamiento y vivos tres años después habian revirado a positivos.

5. Múltiples pruebas de sensibilidad ejecutadas en bacilos tuberculosos obtenidos de 80 enfermos que habían completado 120 días de estreptomicinoterapia revelaron en 80 por ciento de los casos microbios resistentes a más de 10 γ de estreptomicina por cc. No hubo signos de disminución de la incidencia o de la intensidad de la resistencia durante los tres años consecutivos a la terapéutica.

6. Aproximadamente la mitad de los enfermos que manifestaron trastornos vestibulares durante la terapéutica tenían todavía residuos de los mismos a los tres años, sin que en ninguno hubiera empeorado el estado. En 6 por ciento de los pacientes vivos, los médicos examinadores expresaron el parecer de que la gravedad del vértigo o ataxia residual era suficiente para impedir el desempeño de un oficio lucrativo.

Acknowledgment

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DIHYDROSTREPTOMYCIN IN PULMONARY TUBERCULOSIS

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INTRODUCTION

During 1948 dihydrostreptomycin, either as the hydrochloride or the sulfate, became available for clinical trial in human subjects. Four of the New York State tuberculosis hospitals and one of us (H. M. R.) at the Lenox Hill Hospital in New York City undertook the study herein reported for the period May 1948 through July 1949.

The objectives of the study were to determine (a) the therapeutic efficacy of dihydrostreptomycin[2]; (b) toxic effects; (c) the emergence of resistant strains of tubercle bacilli; and (d) to note and appraise other advantages or disadvantages of the drug in the treatment of pulmonary tuberculosis.

Plan of Study

Each participating hospital selected patients for presentation to conferences attended by the investigators for review and decision regarding inclusion in the study. Periodically, accumulated data were reviewed and a group opinion rendered, both as to the effect of dihydrostreptomycin and as to the indications for, and timing of, supplemental forms of collapse or resection therapy. The patients chosen were between the ages of 15 and 60 years, with acute or subacute, predominately exudative, and potentially reversible disease which was moderately or far advanced. A few patients who needed further antibiotic therapy but who were allergic to streptomycin were included. One of us (H. M. R.) acted as chairman of the conferences and coordinator of the study.

Each patient received 40 milligrams of dihydrostreptomycin per kilogram of body weight, administered in divided doses twice daily. The total daily dose was determined at the outset and remained unchanged during the course of treatment irrespective of changes in body weight. Initially the drug was given for ninety consecutive days (26 patients), but effective January 1, 1949 the duration of treatment was reduced to fifty-six days (38 patients).

Prior to the inauguration of drug therapy, each patient had a complete physical examination, standard and special chest roentgenograms as indicated, complete blood count, hemoglobin and blood urea nitrogen determination, sputum examination by both microscopic and cultural methods, urinalysis, audiogram, and caloric stimulation test (Kobrak). Usually these procedures were repeated every two weeks during treatment and monthly thereafter. On each positive sputum culture, sensitivity studies were to be done (Herrold's medium). On a limited number of patients, dihydrostreptomycin blood-level determinations were done. The study was completed in July 1949 and three months allowed to elapse before data were assembled.

[1] From the Hermann M. Biggs Memorial Hospital, Ithaca; the Homer Folks Tuberculosis Hospital, Oneonta; the Mount Morris Tuberculosis Hospital; the Ray Brook State Tuberculosis Hospital; and the Lenox Hill Hospital, New York City.

[2] Supplied through the courtesy of Merck and Company, Inc.

COMPOSITION OF CLINICAL SERIES

Tables 1 and 2 show the age, sex, and disease classification and distribution, and reflect the type of patient selected. Despite the well-recognized difficulty in classifying the disease according to predominant type, it was believed that such should be attempted as a basis for evaluating the efficacy of the drug (table

TABLE 1

Age and Sex Distribution of 64 Patients with Pulmonary Tuberculosis Treated with Dihydrostreptomycin

	TOTAL	MALE	FEMALE
All Ages	64	27	37
Years			
15 to 19	3	1	2
20 to 29	21	4	17
30 to 39	18	7	11
40 to 49	16	12	4
50 plus	6	3	3

TABLE 2

Classification of Pulmonary Disease in 64 Patients at Start of Treatment with Dihydrostreptomycin

	TOTAL	BILATERAL	UNILATERAL
Total	64	52	12
Moderately advanced	30	22	8
Far advanced	34	30	4

TABLE 3

Distribution of Cases Classified According to Predominant Type of Disease

	TOTAL	EXUDATIVE	FIBROTIC	MIXED	CASEOPNEUMONIC
Total	64	44	4	13	3
Acute	15	14	0	0	1
Subacute	38	29	1	7	1
Chronic	11	1	3	6	1

3). This table reflects the intent to select patients with predominantly exudative disease who were either acutely or subacutely ill. The data in table 4 confirms the experience of many that it is impossible to correlate the symptomatology of the patient with the roentgenographic and laboratory findings. Those who denied complaints (6 patients) are grouped with the slightly ill. In general, this corresponds to the description of severity of symptoms appearing in the Diagnostic Standards of the National Tuberculosis Association, 1940 edition.

An attempt was made to determine the age of the "target" lesion either by review of serial roentgenograms when available or on the basis of the history. The age of the lesion could not be estimated with any dependable accuracy in 35 of the 64 cases. Among the remainder were 3 patients whose "target" lesions developed within nine to twelve months preceding treatment, in 11 they developed from four to eight months, and in 15 in less than three months.

On the basis of pretreatment observation, an attempt was made to determine the trend of the disease. In 21 patients there had been no significant demonstrable change in the serial roentgenograms and laboratory and clinical data during several weeks preceding drug therapy. In 33, or approximately half of the total

TABLE 4

Distribution of Cases Classified According to Degree of Clinical Illness

	TOTAL	SLIGHTLY ILL	MODERATELY ILL	SEVERELY ILL
Total	64	31	24	9
Acute	15	3	8	4
Subacute	38	19	15	4
Chronic	11	9	1	1

TABLE 5

Distribution of Cases Classified According to Prevalence of Cavities

	TOTAL	NONE	HONEY-COMB	< 2 CM.	2 TO 4 CM.	> 4 CM.
Total	64	12	3	7	19	23
Acute	15	1	2	1	6	5
Subacute	38	9	0	5	10	14
Chronic	11	2	1	1	3	4

group, the disease was progressive at the time treatment was started. Six patients were resolving their disease at the time medication actually was started, as judged by serial roentgenograms. In 4 patients the problem was so urgent that it was thought advisable to inaugurate antibiotic medication immediately.

Fifty-two of the 64 patients had demonstrable pulmonary cavitation. Of these, 10 had either honeycombing or cavities under two centimeters in total diameter and 42 had cavities more than two centimeters in total diameter (table 5).

Fourteen patients had tuberculous complications. One had a draining sinus of the chest wall, and one had tuberculosis of the urinary tract. The complications in the remaining 12 patients were lesions of the mucous membranes of the respiratory tract, i. e., larynx, trachea, or bronchi.

Fifty-nine of the 64 patients had acid-fast bacilli in the sputum on microscopic examination of direct smears. In 63 of the 64, culture of sputum yielded tubercle bacilli.

RESULTS OF TREATMENT

The results of treatment are reported as evaluated at three specific times: at the end of drug administration, at three months, and again at five months after drug administration. All patients had a minimum of three months post-treatment observation, and 55 were available for evaluation at five months. The patients included in this study were treated with bed rest, dihydrostreptomycin, and such forms of collapse or resection therapy as were indicated. It is extremely difficult, therefore, to determine what quantitative effect any one of the therapeutic factors may have contributed to the total result. In conference, however, the authors made an effort to decide if the change in the patient's condition could be fairly attributed to dihydrostreptomycin.

TABLE 6

Distribution of Cases Classified According to Changes in Cavities Subsequent to Treatment with Dihydrostreptomycin

	TOTAL	NO CHANGE		DECREASED		DISAPPEARED		INCREASED OR NEW CAVITY	
		C	NC	C	NC	C	NC	C	NC
At end of treatment	52	0	14	5	19	8	3	1	2
3 months*	52	2	7	7	8	13	3	7	5
5 months*	46	5	0	5	4	17	5	7	3

* After completion of treatment.
C—Collapse
NC—No collapse

Changes in cavities (table 6): Of the 52 patients who had demonstrable pulmonary cavitation at the start of the study, 14 showed no change in cavity size at the end of treatment; in 3 the cavities were larger; and in 35 the cavities had decreased in size or had disappeared. This result was achieved in 22 patients on bed rest and dihydrostreptomycin alone, whereas the remaining 13 received supplemental therapy, either collapse or resection surgery.

Evaluation of results three months after the cessation of drug treatment shows quite a different picture. At this time 9 patients showed no demonstrable change, in 12 the cavities were larger, and in 31 the cavities were smaller or not visible. Of these 31 in whom no cavity was visible at this time, 11 had achieved this favorable response on bed rest and dihydrostreptomycin alone, but 20 had received supplemental therapy, either collapse or resection surgery.

Forty-six patients had roentgenographically demonstrable pulmonary cavitation at the start of the study and were available for evaluation five months after the drug treatment. By this time only 5 patients had exhibited no change in cavity size, and in 10 the cavities were larger. There remained 31 who had responded favorably. Of these, 9 had achieved this response on bed rest and dihydrostreptomycin alone, and 22 had received supplemental therapy, either collapse or resection surgery.

Effect on tuberculous complications: As previously mentioned, 14 patients had tuberculous complications. Dihydrostreptomycin therapy resulted in moderate improvement in the one draining sinus of the chest wall and marked improvement in one patient with tuberculosis of the urinary tract. Of the 12 patients with tuberculosis of the larynx, trachea, or bronchi, 3 exhibited marked improvement; 5, moderate improvement; and 4, slight improvement.

This duplicated the experience with streptomycin and confirmed the clinical impression that tuberculosis of the mucous membranes responds satisfactorily and often dramatically to dihydrostreptomycin.

Bacteriologic examination of sputum: Although the data available on character and amount of sputum do not warrant detailed tabulation, the evidence strongly

TABLE 7

Results of Bacteriologic Examination of Sputum in 64 Patients Treated with Dihydrostreptomycin

	NUMBER OF PATIENTS			
	Beginning of drug administration	End of drug administration	Three months after completion of drug treatment	Five months after completion of drug treatment
Acid-fast bacilli seen on microscopic examination of direct smear or smear of concentrated specimen	59	44 35 NC 9 C	38 21 NC 17 C	26 14 NC 12 C
Culture of sputum positive for tubercle bacilli	4	8 8 NC – C	8 5 NC 3 C	6 3 NC 3 C
Culture of sputum negative for tubercle bacilli	1*	10 6 NC 4 C	13 7 NC 6 C	19 7 NC 12 C
No data		1 NC	4 3 NC 1 C	12 7 NC 5 C

* Remained culture negative and is excluded from balance of table.
NC—No collapse
C—Collapse

suggests that dihydrostreptomycin had a definite effect in reducing the amount of sputum and in modifying its purulent characteristics.

Table 7 summarizes the data on the bacteriologic examination of sputum at various periods during the study and indicates the number of patients in any category receiving some form of collapse or surgical treatment. The increasing use of supplemental therapy as the study progressed made it impossible to draw any definite conclusions as to the relative effectiveness of the different therapeutic procedures. Nevertheless, in view of the extent and type of disease present at the start of the study, the achievement of negative cultures of the sputum in 30 per cent of those cases previously positive by the end of the five-month period is considered acceptable. It is somewhat discouraging that in 41 per cent of the patients acid-fast bacilli were still present in the sputum at five months in spite of all therapies used. This figure includes those patients who had only a brief period of conversion as well as those who had a relapse.

Emergence of drug-resistant strains (table 8): Complete data on sensitivity studies performed throughout the study and follow-up period are available on 26 patients. Two of these (omitted from the table) had received streptomycin previously and the strains of tubercle bacilli isolated from their sputum were resistant to 1,000 γ per ml. At the start of dihydrostreptomycin therapy these strains were similarly resistant to that drug. One of these patients responded fairly well to dihydrostreptomycin, as judged by changes in the chest roentgenogram. The other continued to have slowly progressive tuberculosis. Of the strains isolated from 24 patients and known to be sensitive at the start, the organisms became resistant to 100 γ per ml. in one patient between the twenty-ninth and forty-second day of treatment, and the patient did poorly. In 8 patients the strains became resistant to 100 γ per ml. between the forty-second and fifty-sixth days of therapy. In 5 of these the disease was progressive, in 2 the response to therapy has been satisfactory, and one left the hospital. In 5 additional patients

TABLE 8

Emergence of Resistant Strains of Tubercle Bacilli in Patients Treated with Dihydrostreptomycin

	NUMBER OF PATIENTS	TIME OF EMERGENCE OF RESISTANT ORGANISM* (DAY OF THERAPY)	GOOD RESULT	POOR RESULT
Patients from whose sputum resistant strains were isolated	1	29 to 42 days	—	1
	8†	42 to 56 days	2	5
	5	57 to 70 days	4	1
	1	90 days	—	1
Resistant strains never isolated	9	—	5	4

* Resistant to more than 10 γ per ml.

† Result in one unknown.

the organisms became resistant to 100 γ per ml. during the fifty-seven- to seventy-day period. Four of these had satisfactory results and one had progressive disease. Only one patient was first found to have resistant organisms three months after drug treatment stopped, and his response was poor. There were 9 patients in whom the organisms remained sensitive to 10 γ per ml. or less throughout the study. A good clinical result was attained in 5 of these, and 4 had progressive disease. It would not seem that any significant conclusions could be drawn from these data.

Toxicity: The only significant manifestations of toxicity were pain, induration, and necrosis at the site of injection. These reactions followed the use of the original shipment of dihydrostreptomycin hydrochloride. Dihydrostreptomycin sulfate did not produce such reactions. It is believed that the reactions were related to impurities. Twenty-nine patients had varying degrees of pain at the site of injection; in 16 some induration developed; and in 3 there was some necrosis at the site.

A few patients complained of such transient symptoms as dermal anesthesia, itching, nausea, vomiting, vertigo, and tinnitus. In no case were symptoms so

severe as to influence medication, nor did they persist. Recovery from all toxic manifestations was prompt and complete.

Because of the interest in late manifestations of deafness, the audiograms done during and after completion of treatment were reviewed with special care. The records were complete in 50 of the 64 cases, 16 of which were followed for a minimum of ten months. Within the so-called normal hearing range, there was no demonstrable loss in acuity from three to ten months after cessation of drug therapy. At the 4,096 frequency there was a loss of 60 decibels in 2 patients, 40 decibels in one patient, and a 10 to 30 decibel loss in 8 patients. There was a gain in hearing acuity of 10 or more decibels in 4 patients. The remaining patients showed no change in acuity of hearing. At the 8,192 frequency there was a loss

TABLE 9

Dihydrostreptomycin in Pulmonary Tuberculosis
Estimated Effect in 64 Patients at End of Drug Therapy

	TOTAL	NO CHANGE	FAVORABLE	WORSE
Classified by Dynamic Status at Start of Treatment				
Total	64 (13)*	14 (2)	46 (10)	4 (1)
Stationary	21 (4)	9 (2)	11 (2)	1
Progressive	33 (9)	3	28 (8)	2 (1)
Retrogressive	6	—	6	—
Unknown	4	2	1	1
Classified by Type of Lesion at Start of Treatment				
Acute	15 (1)	1	13 (8)	1
Subacute	38 (9)	8 (1)	27 (7)	3 (1)
Chronic	11 (3)	5 (1)	6 (2)	—

* ( ) Indicates number of patients who had surgical therapy as well as dihydrostreptomycin.

of 60 to 70 decibels in 6 patients, 20 to 40 decibels in 14 patients, and less than 20 decibels in 2 patients. In no patient, therefore, was clinical deafness manifest.

Estimated total drug effect (tables 9, 10, and 11): At periodic conferences all available data on each case were reviewed and an estimate made of the therapeutic effect of dihydrostreptomycin. Favorable aspects were rated as marked, moderate, or slight. When no favorable response was observed, the result was recorded as no change or worse. Our judgments were based on such factors as abatement of objective symptoms, decrease in fever, alteration in the type and amount of sputum and its bacillary content, degree and rate of roentgenographic changes. Results of treatment were evaluated with reference to the type of lesion at the start of treatment and its dynamic status. This correlation of data was made to determine whether any particular set of circumstances could be expected to result in either a maximal effect of the drug or circumstances in which the drug was relatively ineffective. Irrespective of how the results of treatment are

matched against pretreatment conditions, the same quantitative pattern emerges. The characteristics of this pattern are as follows: The earlier in the pathogenetic phase of the disease the drug was used, the greater the chance of

TABLE 10

Dihydrostreptomycin in Pulmonary Tuberculosis
Estimated Over-all Effect in 64 Patients Three Months following Completion of Drug Therapy

	TOTAL	NO CHANGE	FAVORABLE	WORSE
Classified by Dynamic Status at Start of Treatment				
Total	64 (28)*	8 (2)	38 (18)	18 (8)
Stationary	21 (7)	4	14 (6)	3 (1)
Progressive	33 (17)	2 (2)	16 (8)	15 (7)
Retrogressive	6 (2)	—	6 (2)	—
Unknown	4 (2)	2	2 (2)	—
Classified by Type of Lesion at Start of Treatment				
Acute	15 (8)	2 (2)	9 (4)	4 (2)
Subacute	38 (16)	3	21 (10)	14 (6)
Chronic	11 (4)	3	8 (4)	—

* ( ) Indicates number of patients who had surgical therapy as well as dihydrostreptomycin.

TABLE 11

Dihydrostreptomycin in Pulmonary Tuberculosis
Estimated Over-all Effect in 55 Patients Five Months following Completion of Drug Therapy

	TOTAL	NO CHANGE	FAVORABLE	WORSE
Classified by Dynamic Status at Start of Treatment				
Total	55 (30)*	5 (1)	36 (22)	14 (7)
Stationary	18 (9)	2	12 (6)	4 (3)
Progressive	27 (15)	2 (1)	16 (11)	9 (3)
Retrogressive	6 (3)	—	6 (3)	—
Unknown	4 (3)	1	2 (2)	1 (1)
Classified by Type of Lesion at Start of Treatment				
Acute	12 (7)	2 (1)	9 (5)	1 (1)
Subacute	34 (19)	1	21 (14)	12 (5)
Chronic	9 (4)	2	6 (3)	1 (1)

* ( ) Indicates number of patients who had surgical therapy as well as dihydrostreptomycin.

favorable effect. Second, when a favorable drug effect was observed, it was usually definite, and usually occurred between the fourth and sixth weeks. Changes after this period were comparatively slight and slow. Third, the response was usually slight or absent in patients having chronic disease.

Comparison of the results at the end of drug therapy with results three months and five months after completion of therapy makes it apparent that patients listed as having "no change" progressively decrease in number, whereas the number listed as "worse" progressively increase. There is a steady increase in the number of patients showing a favorable response and a continuing increase in the use of collapse or resection surgery. This makes it impossible to evaluate the effect of dihydrostreptomycin alone.

More suitable conditions for collapse therapy were brought about by dihydrostreptomycin in 17 of 64 patients. The chances for success of collapse therapy were definitely improved in 27 patients, and the period of bed rest was believed

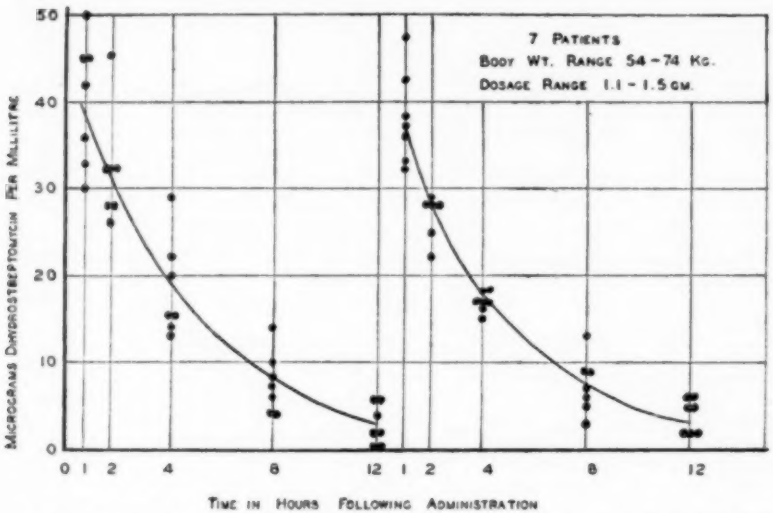

FIG. 1. Concentration of dihydrostreptomycin in serum of patients after doses of 20 γ per kg. of body weight every twelve hours.

to have been shortened also for 27 patients. These favorable results were offset in part by the occurrence of an exacerbation or progression of the disease which, when it occurred, was usually observed during the second to fifth month after the cessation of drug therapy.

Dihydrostreptomycin concentrations in the blood (figure 1): Determinations of the serum concentrations of dihydrostreptomycin were made on samples of blood from 7 patients. The dose of dihydrostreptomycin varied from 1.1 to 1.4 gm. each twelve hours, and the range of body weight was 54 to 74 kg. Blood samples were taken at one, two, four, eight, and twelve hours after each of two consecutive drug administrations. These 7 patients had never previously received streptomycin or dihydrostreptomycin. The serum concentration rose rapidly after drug administration to approximately 40 γ per ml. of serum in one hour.

In four hours the blood level had dropped to approximately 20 γ or one-half of the maximum, and in eight hours had dropped to about 10 γ or one-quarter of the maximum. Determinations at thirty-six and sixty hours after the second drug administration failed to reveal any detectable dihydrostreptomycin in the blood, indicating relatively rapid excretion.

DISCUSSION

In the execution of a clinical study, clinical impressions arise, not readily measurable except in a controlled study, which influence judgment on the value of a therapeutic agent. One such impression gained in this study is that there is a sufficient increment of improvement over and above other forms of therapy to justify the use of dihydrostreptomycin on a broad scale. A second impression is that dihydrostreptomycin rarely constitutes a definitive form of treatment and that relapse of disease following initial improvement does occur (16 in this series). It is believed important that the use of antibiotics should be so correlated and timed with other forms of therapy as to achieve maximum benefit. A third impression is that the patients could frequently distinguish between the hydrochloride and sulfate salt and preferred the latter. A fourth is that a thorough comparative study is desirable to determine the relative value of the various antibiotics available.

SUMMARY

This report summarizes the results of treatment in 64 patients with pulmonary tuberculosis who received dihydrostreptomycin in doses of 40 mg. per kg. per day for fifty-six to ninety days. No significant toxic reactions to the drug were observed except local pain, induration, and necrosis at the site of injection, which were associated only with the use of dihydrostreptomycin hydrochloride.

Dihydrostreptomycin sulfate is a safe and useful therapeutic agent in pulmonary tuberculosis and causes no serious toxic manifestations in the dosage used. Complications of tuberculosis, especially lesions of the mucous membranes of the respiratory tract, responded favorable—often dramatically—to dihydrostreptomycin.

SUMARIO

La Dihidroestreptomicina en la Tuberculosis Pulmonar

Sesenta y cuatro casos de tuberculosis pulmonar fueron tratados con dihidroestreptomicina a dosis de 40 mg. por kg. de peso vivo durante 56 a 90 días. No se observaron importantes manifestaciones tóxicas, aparte de dolor, induración y esfacelo en el sitio de la inyección, y esto únicamente cuando se usó el clorhidrato de dihidroestreptomicina.

El sulfato de dihidroestreptomicina constituye un agente terapéutico inocuo y útil en la tuberculosis pulmonar, sin ocasionar graves manifestaciones tóxicas a las dosis utilizadas. Las complicaciones tuberculosas, y en particular la tuberculosis de las mucosas del aparato respiratorio, respondieron favorable y a menudo dramáticamente a la dihidroestreptomicina.

THE NATURE OF THE ACTION OF STREPTOMYCIN ON TUBERCLE BACILLI[1]

LAWRENCE P. GARROD

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INTRODUCTION

It is helpful in planning the conduct of chemotherapy to understand the nature of its effect on the microorganism. If this effect is merely bacteriostatic, presumably as continuous an action as possible will be desirable. If it is bactericidal, each dose may have a beneficial effect, whatever the interval between it and the next. This aspect of the action of streptomycin in tuberculosis has been remarkably little discussed. In their original paper, Schatz, Bugie, and Waksman (1) credited streptomycin with "strong bactericidal properties," and Smith and Waksman (2) later reported experiments in which the antibiotic in a concentration of only 2 γ per ml. sterilized a culture of avirulent human *M. tuberculosis* in only 6 hours. Streptomycin is certainly actively bactericidal to other species in higher concentrations. Helmholz (3) found that urine containing 1,330 γ per ml. sterilized an inoculum of each of 5 species of bacteria within one hour. Garrod (4) showed that a large inoculum of *Staphylococcus aureus* in broth was extinguished in 8, 4, and 2 hours by concentrations of 20, 50, and 200 γ per ml., respectively; 2,000 γ per ml. produced a 99.8 per cent mortality in only 10 minutes. The writer has also observed by quantitative cultivation at two-hour intervals of urine from patients with urinary tract infection treated with streptomycin that the numbers of living bacteria may be reduced by 99.9 per cent within 2 hours of the first dose, and sterility achieved within 6 or 8 hours when the treatment is successful. The high concentration of the drug attained in the urine is, of course, exceptionally favorable to its action, and such rapid eradication of infection cannot be expected elsewhere in the body.

Despite observations of this kind, it seems to be commonly assumed that the action of streptomycin is at least mainly bacteriostatic. This view is taken in Waksman's recently published book on streptomycin (*Streptomycin. Its Nature and Practical Application*, Williams & Wilkins Co., Baltimore, 1949). Corper and Cohn (5) go so far as to deny that its action in tuberculosis is exerted directly on the bacilli at all, and describe an experiment in which the intermittent introduction of high concentrations into surface cultures in liquid medium failed to arrest growth.

EXPERIMENTAL

The following experiments were made to obtain further information on the effect of streptomycin on *M. tuberculosis*. Streptomycin was added to Dubos liquid medium in various concentrations, and tubes containing 5 ml. were inoculated with 0.2 ml. of a culture in the same medium of *M. tuberculosis* H37Rv.

[1] From the Department of Bacteriology, St. Bartholomew's Hospital, London, England.

The tubes were kept in a water bath at 37°C. and viable counts were made forthwith and at intervals thereafter, using the dropping pipette dilution method and the surface inoculation of Dubos agar medium with a 0.02 ml. drop of each dilution.

The results of one such experiment are shown in figure 1. With both concentrations used there was a fall in the viable count in 2 hours. The fall produced by 100 γ per ml. was steep and sterility was achieved in 8 hours. A concentration of 20 γ per ml. killed more slowly, sterility being demonstrated at 24 hours. In a further series of experiments, using a wider range of concentrations and making counts at intervals of ½, 1, 2, 4, 8, 24, 32, 48, 72, and 96 hours, the following

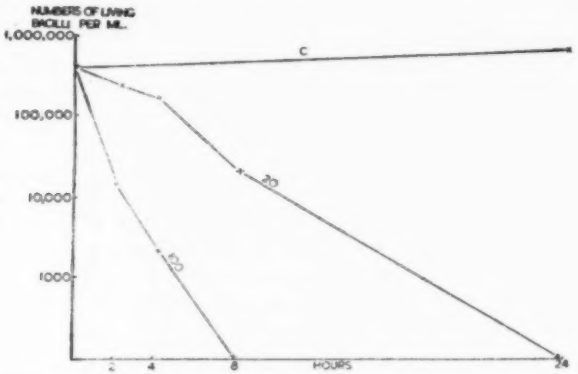

FIG. 1. Viable counts of *M. tuberculosis* H37Rv in Dubos liquid medium at 37°C. containing 100 γ streptomycin per ml., 20 γ streptomycin per ml., no streptomycin ("C").

were the times required to achieve "sterility" (actually to reduce the content of living bacilli to less than 500 per ml., since the first culture was made from a 0.02 ml. drop of a 1 in 10 dilution):

500 γ per ml.	2 hours
100 γ per ml.	8 hours
50 γ per ml.	8 hours
20 γ per ml.	24 hours
10 γ per ml.	72 hours
5 γ per ml.	96 hours

These results are in accord qualitatively with those of Smith and Waksman, although they do not confirm that very low concentrations have so rapid a bactericidal effect.

DISCUSSION

It may be concluded that in a favorable medium streptomycin in concentrations attainable therapeutically throughout the body will cause a substantial

mortality in a population of tubercle bacilli within a few hours. One purpose of this paper is to suggest that this fact may have a bearing on the therapeutic effect of the drug in tuberculosis and particularly on dosage schedules. The original practice was to give several doses daily. Now it is rare to give more than one dose a day, and even intermittent systems, such as two doses per week, have been found satisfactory. It was well established several years ago by Feldman (6) that systems of dosage in guinea pigs, involving short or long intervals and either continuous or intermittent, had an "essentially equal efficacy."

These otherwise anomalous findings can be explained by assuming that a single adequate dose of streptomycin, producing a blood and tissue concentration of 30 γ per ml. or more, does in fact kill a substantial proportion of the actively multiplying and accessible bacilli in the body. It will then be several days before those which were inaccessible in foci of necrosis or frank caseation are able to resume the invasion of surrounding tissues. This hypothesis would account for the success of intermittent treatment, which has been shown to have the further advantage that it delays the emergence of resistance.

The truth of this hypothesis might be tested by enumerating the living tubercle bacilli in the organs of infected guinea pigs shortly after a single dose of streptomycin had been given, control counts being made in animals at the same stage of infection and not so treated. This has not yet been attempted. Some observations by Jensen (7) may appear to have a bearing on this: He made quantitative cultures of the lungs and spleen of guinea pigs heavily infected by inhalation and treated with streptomycin from the third day onward. The numbers of bacilli cultivated from the lungs continued to increase at almost the same rate as in controls until the thirteenth day when they began to diminish, and Jensen's interpretation of this is that streptomycin does not affect the growth of tubercle bacilli in the body until allergy is established. The results of the spleen counts are not given. It seems possible that, in the lungs of animals infected by inhalation, bacilli may have multiplied for some days in the air passages where they would not be subject to the full influence of the drug.

Jensen and others apparently regard the action of streptomycin in the body as differing from that exerted *in vitro*. It is at least a proposition worth considering that the action is of the same nature in either environment. Assuming that this is so, and if it be agreed that to exert a continuous bacteriostatic action is not the aim of treatment but rather that each dose shall have a bactericidal effect, then dosage systems might call for reconsideration. A rational method of treatment, at least for chronic forms of the disease, would be to administer a single large dose or series of doses in one day, aimed at keeping the blood concentration at a high level for, say, 12 hours, at intervals of several days.

SUMMARY

Acting on dispersed cultures of *M. tuberculosis* in a liquid medium, streptomycin is bactericidal; concentrations attainable therapeutically in the body killing a large proportion of the bacilli within a few hours. The possible bearings of this observation on the therapeutic action of streptomycin in tuberculosis are discussed.

SUMARIO

Naturaleza de la Acción de la Estreptomicina sobre los Bacilos Tuberculosos

Al actuar sobre cultivos dispersos del *Mycobacterium tuberculosis* en un medio líquido, la estreptomicina resulta bactericida, destruyendo a las concentraciones obtenibles terapéuticamente en el organismo una gran proporción de los microbios en término de pocas horas.

Se discuten las posibles relaciones de esta observación con la acción terapéutica de la estreptomicina en la tuberculosis.

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THE EFFECT OF STREPTOMYCIN ON TUBERCULOUS MENINGITIS[1]

A Study of Three Cases at Necropsy

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INTRODUCTION

Prior to the advent of streptomycin, tuberculous meningitis was almost universally fatal. With streptomycin, some cures have been reported and the course of the disease in many patients has been lengthened. As with other antibiotics used in treating meningitides, there has been discussion of the value of intrathecal medication. In the case of sulfonamides and of penicillin, this has largely been resolved by the success of treatment of some forms of meningitis without intrathecal therapy (1, 2). The failure of intramuscular streptomycin alone to cure tuberculous meningitis has prompted many workers to give the drug intrathecally as well. This report deals with the morphologic findings in 3 patients with tuberculous meningitis who succumbed to the disease after treatment with streptomycin and with the implication of these findings in relation to intrathecal therapy.

CASE REPORTS

Case 1

Clinical Data

The patient, a 27-year-old-female, was admitted to the hospital in December 1948. Three months before admission she was awakened by a severe frontal headache which was sharp and steady in character. She felt nauseated and vomited. Two days later she again awoke with a severe generalized headache. The headaches continued after this, and soon thereafter she developed backache. After two weeks of daily headache she experienced bilateral tinnitus and pain in the left ear. A sensation of vertigo, with the room spinning, occurred at intervals. She developed anorexia, vomiting, and chills, and was admitted to another hospital. Thereafter she was continuously bedridden. For three weeks she slept most of the time and was later amnesic for this period. She then became more alert, the headaches decreased in severity, but the nausea and vomiting continued.

Physical examination revealed sinus tenderness, soft systolic murmurs over both the apex and base of the heart, possible slight stiffness of the neck, and a left Babinski sign. On lumbar puncture, the initial pressure of the cerebrospinal fluid was 300 mm. of water. The fluid contained 128 erythrocytes and 366 leukocytes per cu. mm., of which 92 per cent were lymphocytes and 8 per cent, polymorphonuclear neutrophils. The cerebrospinal fluid sugar content was 31 mg. per 100 cc. Examinations of the fluid by smears, cultures, and guinea pig inoculation for tubercle bacilli were all negative. A chest roentgenogram revealed left apical and bilateral hilar calcifications.

The patient's temperature ranged from 100° to 101°F. The presumptive diagnosis of tuberculous meningitis was made and the patient was given streptomycin by both the intramuscular and intrathecal routes. The cerebrospinal fluid on different occasions contained an average of 200 leukocytes, of which 90 per cent were lymphocytes. Values of protein were approximately 150 mg. per 100 cc.; and for sugar, 130 mg. per 100 cc. At the end of Novem-

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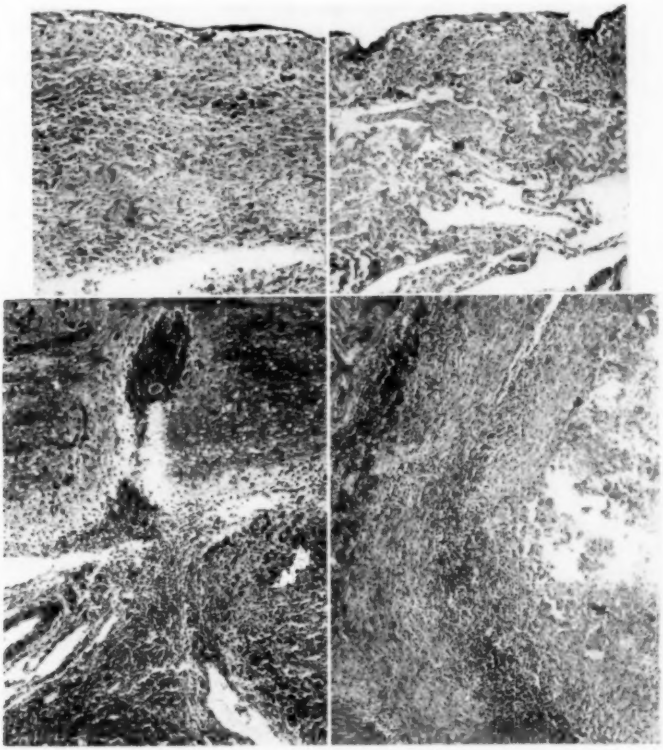
ber 1948, the patient developed severe lumbar pain radiating into the legs. Intrathecal streptomycin was discontinued and the intramuscular dose was raised to 2 gm. per day, following which the root pains disappeared. Tests of vestibular function at this time revealed that the labyrinths did not respond to caloric stimulation. She was transferred to this hos-



FIGS. 1–4. Case 1. (Upper left) Photomicrograph of the lumbar leptomeninges. These are thick and fibrotic and contain scattered lymphocytes. H and E stain. (100×). (Upper right) The leptomeninges in the thoracic region reveal a picture similar to that seen in figure 1. H and E stain. (110×). (Lower left) The pontine substance is at the top, the thick exudate in the leptomeninges at the bottom. Notice the perivascular extension of lymphocytes into the pons. H and E stain. (110×). (Lower right) Caseous necrosis in the exudate in the Sylvian fissure may be seen. H and E stain. (110×).

pital where examination revealed intact cranial nerves. (Labyrinthine function was not tested at this time.) No motor or sensory abnormalities were present. There were hyperactive but equal deep reflexes and a Babinski sign on the left. The patient was unable to sit up because of vertigo.

In January 1949, she became severely ill. The cerebrospinal fluid protein at this time was 210 mg. per 100 cc.; the sugar, 33 per 100 cc.; and there were 100 lymphocytes per cu. mm. Her neck was stiff and Kernig's sign, positive. A report of the finding of acid-fast bacilli in one of 6 guinea pigs was then obtained. She was again given streptomycin, 2 gm. intra-

muscularly and 100 mg. intrathecally each day, and seemed to improve slightly. In March 1949, pneumoencephalogram revealed a slight degree of cerebral atrophy without hydrocephalus. In May 1949 she was discharged to her home. She was fairly well until the end of the month when she became delirious, with severe headache and stiff neck. She was readmitted in a semistuporous state. Cheyne-Stokes respirations appeared, and she died on the day of admission. The total dose of streptomycin was 316 gm. intramuscularly over a period of six and one-half months and 1,450 mg. by the intrathecal route. The duration of illness was nearly nine months.

Autopsy

Gross examination: At necropsy (performed by Dr. William Ruberman), the only evidence of pulmonary involvement was a calcified left apical nodule. Tuberculous lesions were not found in other organs.

The cerebral dura was intact. There were small, milky opacities along the course of blood vessels in the leptomeninges over the convexity of the brain. The meninges at the base were thickened, with impingement on the orifices of the foramina of Luschka. The latter, however, were not completely occluded. A few small tubercles were present in the leptomeninges within the Sylvian fissures.

Except for a moderate cerebellar pressure cone, no cerebral swelling was present. On sectioning the brain, no abnormalities were seen in the cortical gray or subcortical white matter. The ventricular surfaces were covered with numerous small excrescences, giving the ependyma a "dew-drop" appearance. The ventricular system was fully patent and was not dilated.

In the spinal cord, there were many adhesions of the dura to the leptomeninges. This was most prominent in the lumbar region, but was seen throughout the entire length of the cord. The leptomeninges were thickened. No abnormalities of gray matter or of fiber tracts were present.

Microscopic examination: The leptomeninges in the lumbar region (figure 1) were fibrotic and contained only scattered lymphocytes. Neither tubercles nor caseous necrosis were present. The spinal cord in the thoracic region had a similar appearance (figure 2). In the cervical region there were more lymphocytes, but the fibrosis was similar to that seen in the lower regions.

In the leptomeninges overlying the pons, there was extensive cellular exudation which penetrated the pontine substance (figure 3). Numerous lymphocytes as well as caseous necrosis and tubercle formation were seen in the leptomeninges of the Sylvian fissures. This was true of all cortical sections, except for one fibrotic focus in the occipital lobe.

Comment: The morphologic findings in this case demonstrate well a pattern of fibrosis and minimal exudation in the spinal leptomeninges and of caseous necrosis and extensive exudation in the meninges of the brain stem and cerebrum. Long-continued use of intrathecal streptomycin resulted in root pains which disappeared with discontinuance of drug administration by this route.

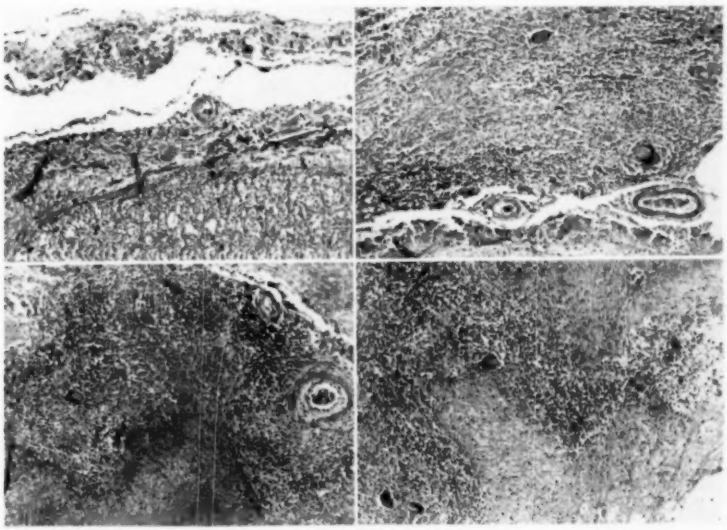
Case 2

Clinical Data

The patient, a 54-year-old male, developed a productive cough with yellow sputum in May 1947. This continued for six months when a roentgenogram of the chest taken at another hospital revealed exudative tuberculosis of the right upper lobe. Hospitalization was advised but refused. In October 1948 he noticed blood-tinged sputum. He continued to work until weakness forced him to enter this hospital in March 1949.

On admission, his temperature was 100° F. Physical examination revealed that the trachea was deviated to the right, the right upper lobe of the lung was dull to percussion, and there were rales throughout the chest. A roentgenogram of the chest now demonstrated far advanced tuberculosis of the fibrocavitary type, involving both lungs. A kinked right

upper lobe bronchus was seen on bronchoscopy without endobronchial disease in the portion visualized. Culture of sputum was positive for tubercle bacilli. In April 1949, intramuscular streptomycin therapy was started with a dose of 1 gm. a day for the first week, and subsequently 1 gm. twice weekly. In June the dose was increased to 1 gm. daily because of lack of improvement. Early in June he complained of low back pain, nausea, and vomiting. This continued until June 28, when he became agitated and disoriented. Neurologic examination revealed definite bilateral papilledema, stiff neck, and a positive Kernig sign. Lumbar puncture was performed and examination of the cerebrospinal fluid revealed the protein content to be 159 mg. per 100 cc.; sugar, 14 mg. per 100 cc.; and chlorides, 362 mg. per 100 cc. There were 5 lymphocytes per cu. mm. and the pressure was 190 mm. of water. Culture of



FIGS. 5-8. Case 2 (Upper left) In the lumbar region, the leptomeninges are fibrotic and contain a few lymphocytes. H and E stain. (150×). (Upper right) The thoracic meninges are thick. Some lymphocytes and two giant cells are present in the dense connective tissue stroma. H and E stain. (120×). (Lower left) Note necrotic zones in the pontine leptomeninges. H and E stain. (120×). (Lower right) In the meninges around the tuber cinereum, caseation and necrosis are evident. H and E stain. (110×).

the fluid was positive for tubercle bacilli. Beginning June 30, 1949, 50 mg. of streptomycin were given intrathecally each day, together with an intramuscular dose of 0.5 gm. On July 22 intrathecal streptomycin therapy was stopped, but intramuscular streptomycin was continued. The patient remained weak and irrational, became dehydrated, and died on September 3, two months after the first symptom of meningeal involvement. The total dose of streptomycin given intramuscularly was 93 gm. administered for four months, and 900 mg. intrathecally during a one-month period.

Autopsy

Gross examination: Necropsy (performed by Dr. John Grühn) revealed fibrocaseous tuberculosis of the upper lobe of the right lung with cavitation, tuberculous mediastinal lymphadenitis, and tuberculous appendicitis.

The cerebral dura was normal. The leptomeninges over the convex surfaces were clear

and translucent. Small yellow masses less than 2 mm. in diameter and resembling tubercles were seen in the leptomeninges surrounding the infundibular stalk. Similar nodules were present in the Sylvian fissures and over the posterior portion of the fourth ventricle. The leptomeninges overlying the pons were cloudy and thick.

On sectioning the brain, the gray matter was normal in appearance. The ventricles were not dilated. The ventricular system was entirely patent. A granular ependymitis was seen throughout the ventricular system. A tubercle was present in the anterior part of the third ventricle just above the optic chiasm. The choroid plexus in the fourth ventricle was thickened. The cerebellum and brain stem were intact.

There were numerous adhesions of the dura to the leptomeninges throughout the length of the spinal cord. The leptomeninges were creamy yellow in color and thick. There were no abnormalities of the central gray matter nor of the fiber tracts.

Microscopic examination: The pia-arachnoid in the lumbar region was fibrotic (figure 5). There were a few scattered lymphocytes, but no other evidence of activity of the tuberculous process. At the thoracic level of the spinal cord the leptomeninges were thickened and contained a moderate number of lymphocytes and a few giant cells (figure 6). The thickening of the leptomeninges, however, was secondary to fibrosis without caseous necrosis. Caseation was present in the leptomeninges overlying the pons (figure 7). Tubercles and extensive tuberculous angiitis were present in this region. As a result of the angiitis there was a small infarct in the pons. The choroid plexus contained tubercles. Numerous active tuberculous lesions were seen in the cerebrum. One example of these lesions, in which there may be seen both caseation and necrosis, is shown in figure 8.

Comment: It is of interest that this patient developed tuberculous meningitis while receiving streptomycin by the intramuscular route. This occurrence indicates that, if this drug is to be effective, either higher doses or other routes of administration must be used. The histologic evidence of fibrosis and healing low in the spinal cord contrasts strikingly with the exudation, angiitis, and necrosis higher in the neuraxis.

Case 3

Clinical Data

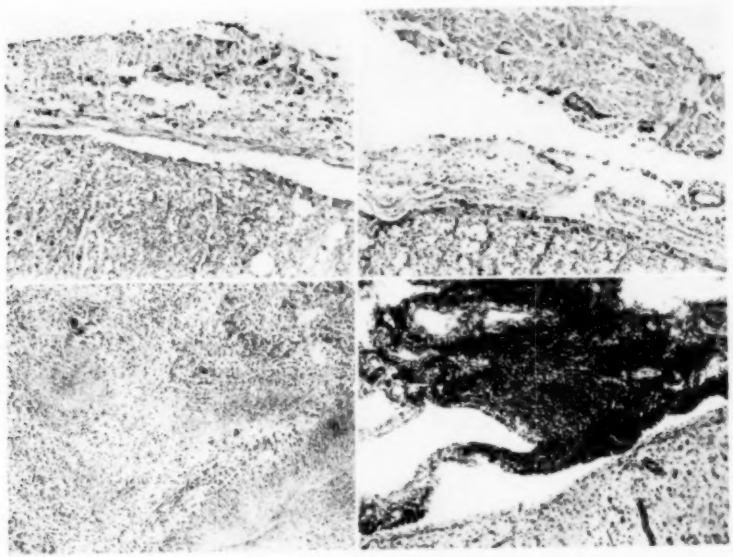
The patient, a 56-year-old white male, had a history of cough for five years and three episodes of hemoptysis in the three years preceding admission. Five months before admission he developed "flu." Thereafter his cough became more productive, and he became increasingly weak. A roentgenogram of the chest revealed far advanced bilateral pulmonary tuberculosis with cavitation and extensive pleuritic changes. When admitted to the hospital in April 1948, the sputum was found on microscopic examination to contain acid-fast bacilli. It was decided to treat him by bed rest, and he was ultimately discharged to his home in November 1948.

Three weeks later he began to lose his appetite and he developed severe frontal headaches which prevented him from sleeping. He became irritable, weak, and dizzy, and finally drowsy and disoriented. He was readmitted in December 1948. Examination revealed a temperature of 101 F. Wheezes and rales were heard throughout the chest. There was minimal bilateral papilledema. The neck was only slightly rigid. There were positive Kernig signs bilaterally. The patient was oriented, but sleepy. Lumbar puncture revealed a cerebrospinal fluid pressure of 280 mm. of water. The cerebrospinal fluid sugar content was 38 mg. per 100 cc. and there were 50 lymphocytes per cu. mm.

He was given streptomycin in doses of 1 gm. intramuscularly twice daily and 50 mg. intrathecally every two days. The cerebrospinal fluid was studied during the following five months of therapy without revealing definite trends in the values obtained in the various examinations made. The initial pressure ranged from 180 to 420 mm. of water. The cell count ranged from 2 to 226 per cu. mm., tending to be lower after the first month. The protein content ranged from 90 to 225 mg. per 100 cc.; the chlorides, from 341 to 393 mg. per 100

cc.; and the sugar, from 25 to 78 mg. per 100 cc. Culture of the cerebrospinal fluid revealed tubercle bacilli only on the third day of treatment and was thereafter negative. Roentgenograms of the chest showed few changes throughout his hospital stay.

He seemed to improve symptomatically, and in March 1949 was up in a wheel chair. In April headache recurred. In May he developed confusion, disorientation, and hallucinations. Neurologic examination was similar to that performed on admission. He became progressively more somnolent and cyanotic, and died in May 1949. The total dose of intramus-



FIGS. 9-12. Case 3. (Upper left) In the lumbar region of the spinal cord there are a few lymphocytes contained in the proliferated leptomeninges. H and E stain. (150×). (Upper right) Fibrosis of the thoracic leptomeninges may be noted. H and E stain. (150×). (Lower left) In the pontine meninges extensive necrosis is present. H and E stain. (120×). Massive exudation may be seen in the meninges of temporal lobe. Nissl stain. (120×).

cular streptomycin administered was 284 gm. over a four-month period, and 3,500 mg. intrathecally in the same period of time. The duration of illness was slightly more than four months.

Autopsy

Gross examination: At necropsy (performed by Dr. William Ruberman) bilateral chronic fibrocavitary pulmonary tuberculosis was found. The cerebral dura and dural sinuses were normal. The leptomeninges over the convexity were thin and clear. Numerous tubercles were present at the base of the brain over the hippocampal gyri, the orbital gyri, in the Sylvian fissures, in the median longitudinal fissure of the frontal lobe, and in the cerebellopontine angle. The leptomeninges overlying the pons and cerebellum were thickened.

The gray and white matter appeared normal on sectioning the brain. The ependymal surfaces of lateral and third ventricles contained numerous small excrescences, giving a "dew-drop" appearance. Hydrocephalus was not present. Brain stem and cerebellum were unremarkable in the gross.

Ventrally, there were only a few adhesions of spinal dura to the pia-arachnoid, but dorsally many adhesions were present. The leptomeninges in the region of the cauda equina were thickened. The gray matter and fiber tracts were not abnormal.

Microscopic examination: There was fibrosis of the leptomeninges in the lumbar region of the spinal cord (figure 9). Only a few lymphocytes were seen. A similar picture was present at thoracic levels (figure 10). In the meninges of the medulla and pons, however, exudation and caseation were prominent (figure 11). A lymphocytic ependymitis was present in the aqueduct, but the orifice was widely patent. Numerous tubercles, exudation (figure 12), meningitis, and angiitis were present in the cerebrum. The choroid plexus contained only a few small lymphocytic infiltrations.

DISCUSSION

In the past, the course of tuberculous meningitis was so uniformly progressive that the findings in the spinal cord herein described were not encountered. Tuberculous meningitis healing with fibrosis is a new entity. The almost exclusive limitation of the fibrosis to the spinal cord is a consistent and striking fact. This observation was noted in some of the cases reported briefly by the British Medical Research Council (3). It is highly probable that the direct administration of streptomycin in this region of the neuraxis was in large part responsible for the appearance of the lesions in these cases. It may be assumed that the therapeutic effect of the drug on the inflammatory process was to produce healing by fibrosis. The possibility also exists that the irritative effect of streptomycin on the leptomeninges contributed to the formation of scar tissue.

The intrathecal administration of drugs may well be harmful. There are numerous reports in the literature to attest to this fact (4). Both sulfonamides and penicillin are effective in the treatment of various meningitides without intrathecal medication. In the use of streptomycin in tuberculous meningitis, however, the best results have been obtained with combined intramuscular and intrathecal administration. Most of the patients reported as cured received the drug by both routes (5, 6). In a series of cases described by the Medical Research Council (3), better results were obtained with combined therapy than by the intramuscular route alone. Case 2 of the present series demonstrates that infection of the meninges by tubercle bacilli may occur *during* intramuscular therapy.

It appears then that intrathecal streptomycin is of value, especially in aiding healing in the spinal meninges. It seems probable, therefore, that some means of obtaining higher concentration of the drug in the upper portion of the neuraxis would be helpful. This has been attempted by Cairns, Duthie, and Smith (7) who utilized the intraventricular route. Indeed, Smith, Vollum, and Cairns (8) have even administered streptomycin by indwelling catheter to the interpeduncular space and basal cisterns. The results of these attempts are not yet available. Another means of delivering higher concentrations of streptomycin to the upper neuraxis might be achieved by placing the patient in the Trendelenburg position after intrathecal injection in the lumbar region. It is recognized that the use of intraventricular streptomycin or high concentrations of the drug over the cortical surfaces is not without danger. Nevertheless, if the drug is to be used,

either higher doses, other portals, or combination with other drugs are needed to raise the cure rate. In an otherwise uniformly fatal disease, such attempts are worthy of trial.

SUMMARY AND CONCLUSIONS

This report describes the observations at necropsy in 3 patients with tuberculous meningitis who were treated with intramuscular and intrathecal injections of streptomycin. Post-mortem examination revealed the relatively new entity of tuberculous meningitis with fibrosis and minimal exudation in the leptomeninges of the spinal cord. This appearance was in contrast with an active process of exudation and necrosis in the meninges of the brain stem and cerebrum. It is believed that the higher concentration of streptomycin in the spinal meninges was responsible for the healing. Other evidence of the value of intrathecal streptomycin is presented. An effort should be made in future regimens of treatment to deliver higher concentrations of streptomycin to the brain stem and cerebrum.

SUMARIO Y CONCLUSIONES

El Efecto de la Estreptomicina sobre la Meningitis Tuberculosa

Tres enfermos con meningitis tuberculosa fueron tratados con estreptomicina por las vías intramuscular e intratecal. La autopsia reveló una entidad relativamente nueva de meningitis tuberculosa con fibrosis y exudado mínimo en las leptomeninges de la médula espinal, lo cual contrastaba con un proceso activo de exudado y necrosis en las meninges del bulbo raquídeo y del cerebro. Parece que la concentración mayor de estreptomicina en las meninges raquídeas fué la causa de la cicatrización. Preséntanse otras pruebas del valor de la estraptomicina intratecal. Hay que hacer un esfuerzo para llevar mayores concentraciones de estreptomicina a la médula oblongada, el puente de Varolio y el cerebro.

Acknowledgment

The photomicrographs used in this series were prepared by Antol Herskovitz.

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ALVEOLAR CELL TUMOR OF THE LUNG[1]

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INTRODUCTION

Alveolar cell tumor of the lung is a rare tumor. In 1942, Neubuerger and Geever (1) found in the literature reports of 25 cases of unmistakable gross and microscopic evidence of alveolar cell tumor. Subsequently several additional cases have been reported. During the period of one year, 5 cases diagnosed by pathologists as alveolar cell tumor came to our attention. In retrospect there seem to have been some similarities in the clinical and radiologic findings in these cases. It is the purpose of this paper to summarize the clinical, radiologic, and pathologic findings in the hope of aiding in the future clinical diagnosis of this condition.

CASE REPORTS

Case 1

Clinical Data

A. H., an 83-year-old white housewife, was admitted to the hospital on September 23, 1946. She gave a history of shortness of breath, increased fatigue, and anorexia for three weeks. She had lost "considerable" weight in the past month. She had had no pain, edema, cough, or expectoration. There was no family history of cancer. Examination revealed a poorly nourished woman with a rapid respiratory rate propped up in bed. The lungs were resonant to percussion, tactile fremitus was normal, the breath sounds were harsh vesicular, and no rales or rubs were heard. The heart was enlarged to the left, and the first sound was accentuated at the mitral area. The blood pressure was 110 systolic, 68 diastolic in mm. of mercury.

Laboratory examination revealed a leukocyte count of 18,600 per cu. mm. with a shift to the left in the differential count. The erythrocyte count and hemoglobin concentration were normal. A urinalysis was negative. An electrocardiogram showed sinus tachycardia and evidence of myocardial damage, with low voltage and slurred QRS complexes but upright T waves. A roentgenogram of the chest showed irregular, conglomerated areas of increased density involving the greater part of both lung fields, with some enlargement of the heart. These findings were interpreted as marked pulmonary congestion and edema. During her hospital stay the temperature varied from normal to 101°F., the pulse varied from 68 to 112 per minute, and the respiratory rate from 20 to 40 per minute. The patient was given oxygen by nasal tube and also received morphine. She became quite dyspneic and developed marked cyanosis in spite of oxygen therapy. Digitalis was administered but there was no improvement. She developed crepitant rales throughout both lung fields, most marked in the left lower lobe, and was then thought to have pneumonia, possibly of viral origin. She was given penicillin, oxygen under positive pressure, and coramine, but became rapidly worse and died. The clinical diagnosis was arteriosclerotic heart disease with pulmonary congestion and pneumonia, possibly of viral etiology.

Autopsy

Gross examination: There were dense adhesions at the apices of both lungs and approximately 100 cc. of clear yellow fluid in each pleural cavity. The lungs felt nodular and resist-

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FIG. 1. Case 1. Roentgenogram of the chest. Irregular conglomerated areas of increased density involve the greater part of both lung fields. Interpreted as pulmonary congestion and edema.

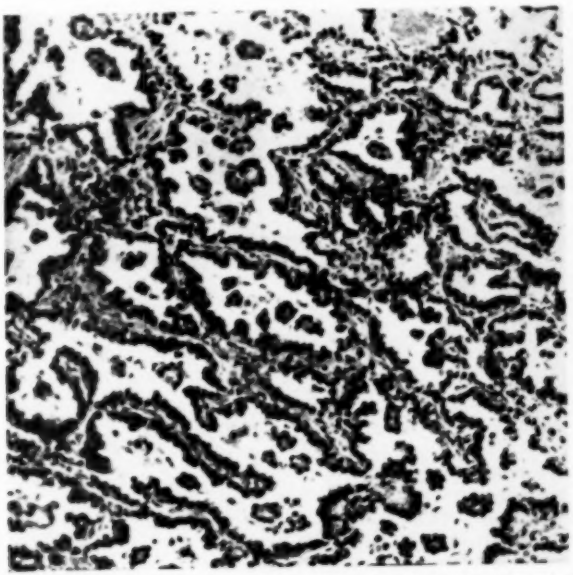

FIG. 2. Case 1. Photomicrograph of the lung. The alveoli are lined by cuboidal and low columnar epithelial cells with large, round, hyperchromatic nuclei. Mitoses are frequent, but mucous secretion is not observed.

ant to palpation throughout. The right lung weighed 910 gm. and the left, 920 gm. On cut section, many grayish-white nodular areas were present from 2 mm. to 8 mm. in diameter, scattered diffusely throughout both lungs. The bronchi and peribronchial nodes showed no evidence of involvement by tumor. No metastases were noted and no extrapulmonary focus of malignancy was found. The heart weighed 350 gm. The right side of the heart, particularly the atrium, was markedly dilated. There were sclerosis and calcification of the mitral valve and arteriosclerosis of the aortic valve.

Microscopic examination: The usual alveolar lining cells of the lungs were replaced by cuboidal or low columnar epithelial cells with large, round hyperchromatic nuclei. Mitoses were frequent among these cells. A few multinucleated tumor giant cells were present. There were frequent clumps of these epithelial cells lying free in dilated alveolar spaces. Many neutrophils were also found in the alveoli, and a few were scattered through the stroma. The stroma was fibrous and of medium density, and considerable black pigment was seen in some areas. This appearance prevailed throughout all sections taken. The bronchiolar epithelium showed no neoplastic changes. No lymphatics were seen to be invaded.

FIG. 3. Case 2. Roentgenogram of the chest. An infiltrative process is present through both lungs with cyst formation in some areas. Interpreted as lung cyst with infection.

Case 2

Clinical Data

B. B., a 70-year-old white female, was admitted to the hospital on December 4, 1945. She gave a history of chronic cough and expectoration for two years, with loss of fifteen pounds in weight. During the month before admission she had had an irregular fever up to 102° F., her expectoration had become more profuse, and she had had moderate dyspnea. One brother had died of cancer of the lung. Examination revealed a poorly nourished woman with slight cyanosis. There was some impairment of resonance at the left base, but

fremitus was normal. There were wheezes throughout both lung fields and scattered crepitant and subcrepitant rales, most marked in both bases posteriorly.

Laboratory examination revealed a moderate anemia, a leukocyte count of 7,150 per cu. mm., and a shift to the left on the differential count. Urinalysis and Kahn test were negative. Total serum proteins and albumin-globulin ratio were normal. Several examinations of sputum were negative for acid-fast bacilli and spirochetes. Roentgenographic examination of the chest was interpreted by the radiologist as showing an infiltrative process through both lungs with cyst formation in some areas. The patient was treated with penicillin injections and aerosol penicillin. She was discharged somewhat improved, with a diagnosis of primary atypical pneumonia.

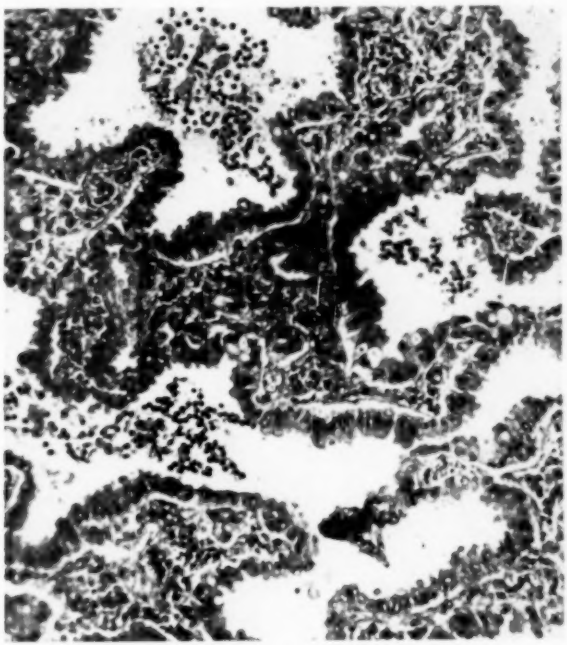

FIG. 4. Case 2. Photomicrograph of the lung. There is a cuboidal to high columnar epithelium lining the alveoli. The cells have active mucous secretion. The interalveolar septa are moderately thickened.

She was readmitted eight days later because of chills and fever. She was found to be acutely ill, markedly dyspneic and cyanotic, with some orthopnea. The percussion note was impaired over the left lower lobe posteriorly. The breath sounds in this area were bronchial in character. Vocal fremitus was increased over the left lower lobe posteriorly. There were coarse bubbling rales over both lung fields. The pulse was irregular. Laboratory examination again revealed a moderate anemia with a leukocyte count of 4,100 per cu. mm., with a normal differential count. A roentgenogram of the chest showed an extension of the pneumonia on both sides with considerable involvement of the left lower lobe by more chronic disease and considerable involvement of the right upper lobe by a new process. This

was interpreted as lung cyst with infection. She was given penicillin by injection and oxygen. Several attacks of pulmonary edema occurred and aminophylline was given intravenously, with some relief. Digitalis was given, with no particular benefit. During her hospital stay her temperature varied from 99° to 103.5°F., her pulse varied from 100 to 140 per minute, and her respiration varied from 22 to 48 per minute. She died in an attack of pulmonary edema. The final clinical diagnosis was primary atypical pneumonia and pulmonary edema.

Autopsy

Gross examination: The right pleural cavity contained approximately 55 cc. of opaque reddish fluid. The pleural cavity showed prominent whitish lymphatics and a number of fibrous bands attaching the lungs to the thoracic walls. In addition, the right pleura showed some dense white patches under which the lung was contracted. Both lungs together weighed 1,580 gm. Both lower lobes and about one-third of each upper lobe showed almost complete consolidation. The right middle lobe was crepitant. On cut surface the consolidated areas were of gray color. Scattered over the consolidated areas, particularly near the pleural surface, were firmer areas which showed a more whitish color. The bronchi and mediastinal nodes showed no tumor. No metastases were noted. No primary focus of malignant neoplasm was found outside of the lung.

Microscopic examination: The alveoli of the lungs were packed with an exudate of polymorphonuclear and mononuclear leukocytes and some fibrin. Practically all alveoli were lined by epithelium which varied from cuboidal to high columnar, which often formed papillary projections into the lumina and which sometimes showed active mucous secretion. The interalveolar septa were moderately thickened.

Case 3

Clinical Data

A. V., a 57-year-old white female teacher, was first admitted to the hospital on July 15, 1946. Her chief complaints were a dull pain in the right chest for nine months and a weight loss of five pounds. She had been hospitalized at a local hospital three months previously, and one quart of clear fluid had been removed from the right chest. There had been no complaint of cough, expectoration, or hemoptysis. She had had two episodes of diarrhea during the previous winter. Examination revealed dullness to percussion over the right lower lobe, and a friction rub was heard in this area. There were many fine rales posteriorly in the right chest. Intercostal tenderness was found at the left lower chest. The blood pressure was 110 systolic, 65 diastolic in mm. of mercury, and the heart was normal.

Laboratory examination revealed a normal erythrocyte count, a leukocyte count of 6,750 per cu. mm., and a normal differential count. Kahn test, urinalysis, and stool examinations were negative. The total serum proteins and the albumin-globulin ratio were normal. An electrocardiogram was normal. Several examinations of sputum showed no acid-fast bacilli and no abnormal cells. Cold agglutinins were positive in a dilution of 1:20. A roentgenographic examination of the chest revealed an infiltrative process in the right middle lobe. Bronchography revealed incomplete filling of the bronchial tree in the right middle lobe, with the other major bronchi normal. These findings were interpreted as partial atelectasis of the right middle lobe, possibly due to bronchogenic carcinoma. Bronchoscopic examination revealed reddened mucosa which was edematous and bled easily. There was some secretion from the right side but no tumor tissue was seen. Her temperature varied from normal to 99.4°F., pulse from 68 to 100 per minute, and respirations from 16 to 24 per minute. The patient was discharged from the hospital with her condition unchanged and with a diagnosis of atypical pneumonia.

She was readmitted six weeks later (September 9, 1946) complaining of increasing right

pleuritic chest pain. She had developed a constant hacking, nonproductive cough. On one occasion she had expectorated a small amount of sputum slightly tinged with blood. She had gained about five pounds in weight. Examination revealed some splinting of the right lower chest; breath sounds, vocal fremitus, and tactile fremitus were diminished over the same area. Some inspiratory clicking rales were heard in the right chest. A few cervical lymph nodes were palpable and the liver was palpable and tender.

Laboratory examination gave results similar to those during her first admission. A right thoracentesis was done, and 60 cc. of serosanguineous fluid and a little air were removed

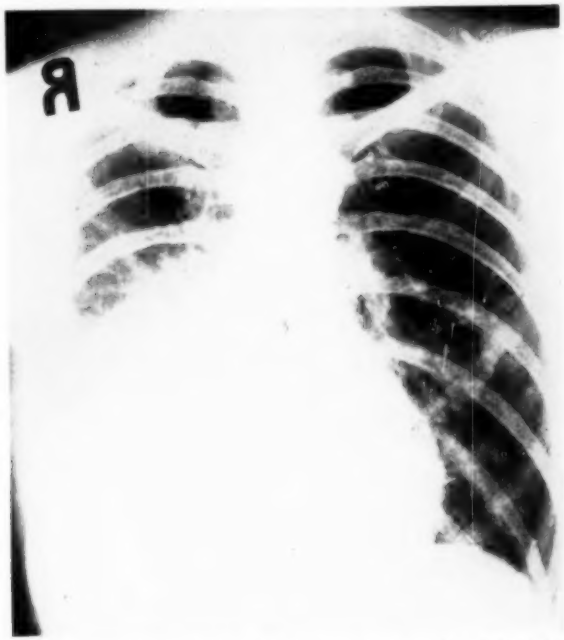

FIG. 5. Case 3. Roentgenogram of the chest. There is an opacity of the right lung thought to be the result of atelectasis and fluid. Interpreted as bronchogenic carcinoma.

when the procedure had to be stopped because of a reaction to procaine. Culture of the chest fluid yielded no growth, and no cancer cells were found in the fluid. Two bronchoscopic examinations revealed an area of granular tissue at the middle lobe orifice which was friable and bled easily. Microscopic examination of biopsy specimens showed chronic inflammation. A roentgenogram of the chest revealed complete opacity of the lower right chest below the level of the third rib anteriorly, thought to represent atelectasis and fluid. An exploratory thoracotomy was done, with removal of the sixth rib on the right. The lung was found to be fixed and scarred, and curious small granulations could be seen throughout the chest cavity over the surface of the lung and the pleural wall itself. These granulations were firm and measured 1 to 2 mm. in diameter. A large amount of bloody fluid was found in the pleural cavity. Both pleural surfaces were studded with small hard nodules. The appearance of these nodules was strongly suggestive of miliary carcinomatosis, although

they differed from cancer nodules, especially in the fact that they were more gray than white. In view of the extensive infiltration of both surfaces of the pleura with nodules, it was obvious that a radical operation would accomplish nothing. Moreover, operation would have been almost impossible to perform because of the marked distortion and scarring of the hilus. Microscopic examination of a frozen section of tissue obtained by biopsy was reported to reveal a granuloma of unknown nature. The chest was closed. The preoperative diagnosis had been carcinoma of the lung. After further study of the sections made from the biopsy specimen, the postoperative diagnosis was alveolar cell carcinoma of the lung. Postoperatively, the patient was given penicillin injections, blood transfusions, and plasma. She was discharged from the hospital with her condition essentially unchanged. This patient died in July 1947, but no autopsy was done.

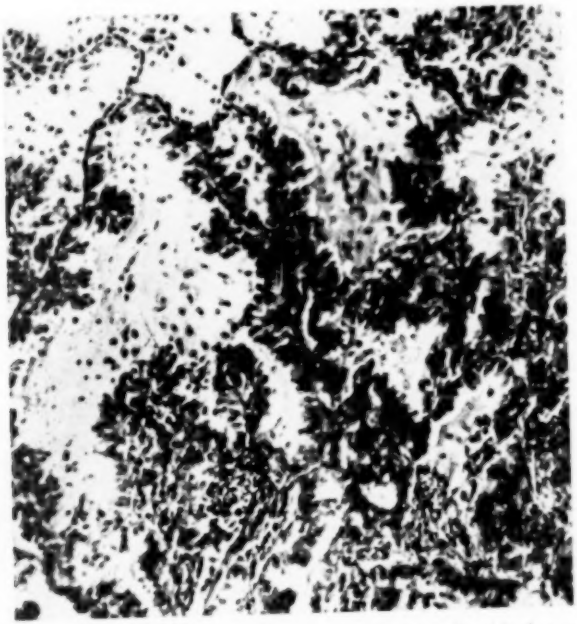

FIG. 6. Case 3. Photomicrograph of the lung. The alveoli are lined by low-to-tall columnar epithelial cells usually in a single layer but occasionally in several layers. Many of the cells have active mucous secretion.

Pathologic Examination of Biopsy Specimen

Microscopic examination: The alveolar walls were lined by columnar epithelial cells, ranging from low to tall, and arranged usually in a single layer but occasionally in several layers. Many of these cells showed active mucous secretion. The lumen contained serum or mucus and moderate numbers of lymphocytes. The stroma was of moderate density and infiltrated by lymphocytes.

Case 4

Clinical Data

I. C. P. was a 75 year old white housekeeper, admitted to the hospital on May 25, 1946. The chief complaints were a cough productive of moderate amounts of whitish foamy sputum

and dyspnea for one month. She also complained of night sweats, weakness, and fever to 100°F. She had lost fifteen pounds in weight but had been on a reducing diet. Some palpitations had been experienced. There was a family history of tuberculosis and possible cancer. Examination revealed a fairly well-nourished woman with limitation of expansion of the chest and with some dyspnea. There was dullness to percussion over the right scapula, tactile fremitus was increased over the right side posteriorly, the breath sounds were vesicular, and there were coarse rales at the right apex. There was no clubbing of the distal phalanges or cyanosis. The blood pressure was 126 systolic, 89 diastolic in mm. of mercury.

Laboratory examination revealed a leukocyte count of 13,700 per cu. mm., with a normal differential count and no anemia. Urinalysis was negative. Repeated blood counts were essentially the same as on admission. Three sedimentation rates were 78, 87, and 85 mm. per

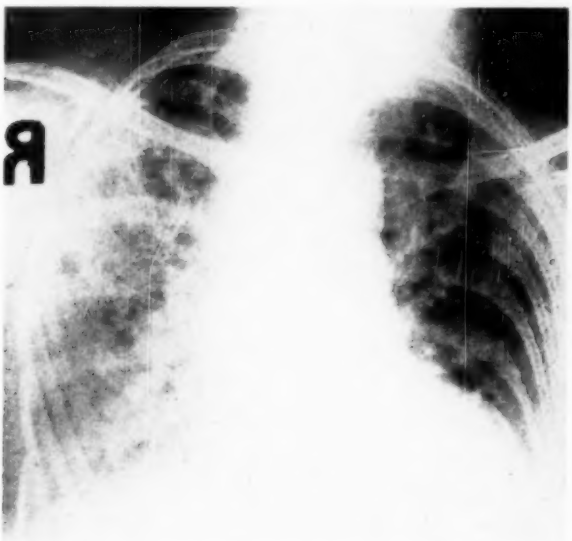

FIG. 7. Case 4. Roentgenogram of the chest. A mottled infiltration is present throughout the entire right lung and a similar process in the upper portion of the left lung. Interpreted as lung infection, probably tuberculosis.

hour. Many sputum examinations were negative for acid-fast bacilli, yeast forms, *Actinomyces*, fungi, and spirochetes. Examination of smears of sputum showed many pus cells, gram-negative bacilli, and gram-negative *Diplococci*, probably *Micrococcus catarrhalis*. Culture of sputum showed gram-negative bacilli and cocci. Agglutination tests on the patient's serum gave the following results: Paratyphoid B, positive 1:320; Typhoid (H), positive 1:80; others, including Proteus OX19, negative. Blood cultures were sterile. Determinations of serum proteins, albumin-globulin ratio, and blood calcium were normal. Roentgenographic examination of the chest showed a mottled infiltration throughout the entire right lung, and a somewhat similar process took place in the upper portion of the left lung. The heart was slightly enlarged. It was thought that these infiltrations represented some type of lung infection, probably tuberculosis.

The patient was given penicillin by injection and by aerosol. Nasal oxygen was given with some relief. She gradually became cyanotic, the neck veins became engorged, and she

became lethargic. Orthopnea and tachypnea were observed. Loud moist rales became audible throughout both lung fields, and the patient died in respiratory failure. During her hospital stay the temperature varied from normal to 100.2°F., respirations varied from 36 to 86, and the pulse varied from 84 to 110 per minute. The final clinical diagnosis was pulmonary infection of undetermined etiology.

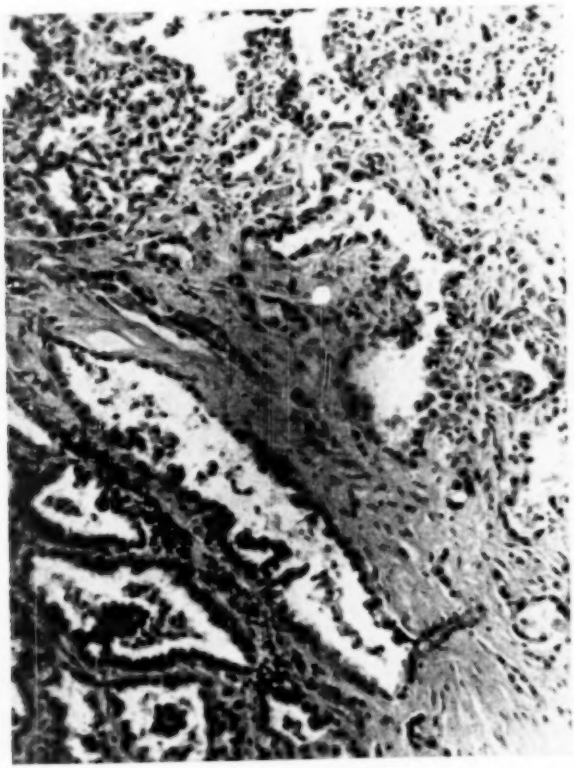

FIG. 8. Case 4. Photomicrograph of the lung. The alveoli are lined by cuboidal-to-columnar hyperchromatic epithelial cells, many of which are vacuolated and have active mucous secretion.

Autopsy

Gross examination: No fluid was found in either pleural cavity. Throughout both lungs there were firm, gray, rounded nodules up to 1.5 cm. in diameter. Bronchi showed dark mucoid material but no tumor. Peribronchial nodes were large and black but showed no tumor. There were [illegible] metastases. No primary focus of malignancy was found outside of the lung.

Microscopic examination: In all sections taken throughout both lungs there were areas of organizing pneumonia with granulation tissue infiltrated by lymphocytes, plasma cells, and mononuclear macrophages. There was resultant atelectasis of many of the alveoli in these areas. Many of the alveoli were lined by flattened or cuboidal epithelial cells, many

of which were vacuolated. Other alveoli were lined by hyperchromatic, tall, columnar cells, many of which showed active mucous secretion. Mitotic figures were rare. There was no evidence of neoplasm of the major bronchi.

Case 5

Clinical Data

E. E., a 78-year-old white female housewife, was admitted to the hospital on August 6, 1946, and died August 7, 1946. She had complained of a chest cold for two months. The dyspnea which she had had for two years had greatly increased in the past two months and she began to notice ankle edema. She also had developed a pain in the left chest and

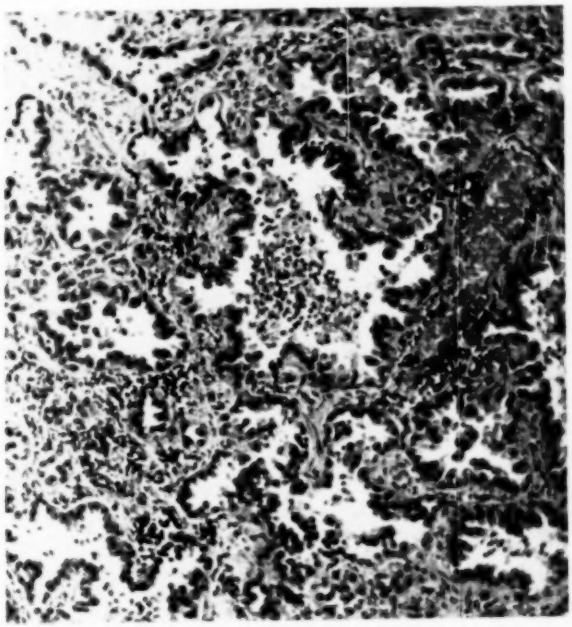

FIG. 9. Case 5. Photomicrograph of the lung. Anaplastic cells, usually cuboidal in shape, line the alveoli. The cells have scanty cytoplasm and large hyperchromatic nuclei with frequent mitotic figures. Many contain prominent nucleoli. Mucous secretion is not observed.

upper abdomen. On several occasions the patient had expectorated blood. She had been given digitalis, with some improvement, and had remained up and about. There was no family history of cancer. Examination revealed a fairly well-nourished woman, apprehensive and alert, in acute respiratory distress. The pharynx was moderately engorged. The anteroposterior diameter of the chest was increased from the normal. There were engorgement of the neck veins and cyanosis. Resonance was impaired on the left side, breath sounds were diminished on the left, and moist rales were heard at both bases posteriorly, more numerous on the left. The heart was enlarged to the left, the sounds were of poor quality. The rhythm was grossly irregular and was thought to be auricular fibrillation. The blood

pressure was 120 systolic, 72 diastolic in mm. of mercury. The liver was 2 cm. below the right costal margin, but there was no definite ankle edema. A leukocyte count was 8,200 per cu. mm., with a slight shift to the left in the differential count. There was moderate anemia. The urinalysis was negative. The patient was given morphine, digitalis, and oxygen by nasal tube, but rapidly became more dyspneic and died in acute respiratory failure. While in the hospital her respirations varied from 30 to 40 per minute, her temperature from 97° to 100° F., her pulse from 88 to 96 per minute. The final clinical diagnosis was arteriosclerotic heart disease with cardiac failure.

Autopsy

Gross examination: There were 750 cc. of blood-tinged fluid in the left pleural cavity. Many old fibrous adhesions were found between the pleural surfaces of the left lung and the parietal pleura. No adhesions or fluid were found in the right pleural cavity. The lungs together weighed 720 gm. There were many fibrous band-like adhesions hanging from the pleural surfaces of the left lung. The entire pleural surfaces of the left lung were thickened. The left lung was suberepitant with patchy areas of firm consistence in both lobes. On cut section the parenchyma was a dark reddish-purple in color. There were many whitish-gray areas seen around the bronchi and at the periphery of the lobes. The pleural surface of the right lung showed no adhesions. The three lobes of the right lung had an increased rubbery consistence. On cut section through the right lung, several of the branches of the pulmonary artery contained blood clots which were adherent to the wall of the artery. At the periphery of the lobes several dark red areas stood out from the reddish-purple parenchyma of the remainder of the lung. The bronchi contained no tumor growth. No metastases were noted. No primary focus of malignancy was found outside of the lung.

Microscopic examination: The alveolar walls of the lungs were lined by anaplastic cells usually cuboidal in shape and arranged in single layers. They had scanty cytoplasm and large hyperchromatic nuclei which varied considerably in size. Many contained prominent nucleoli. Mitotic figures and multinucleated tumor giant cells were common. Many of these lining cells were lying loose within alveoli along with a few lymphocytes and mononuclear macrophages. In many areas the appearance was that of organizing pneumonia with replacement of parenchyma by granulation tissue in which there were many lymphocytes and mononuclear macrophages.

Etiology and Histogenesis

The etiology of alveolar cell tumor is as obscure as that of many other forms of neoplasm. Bonne (2) suggested a viral origin because of the morphologic similarity to jaagziekte, a disease of sheep in which there is pulmonary adenomatosis. The latter disease occurs in epidemics, and from the work of Dungal, Gislason, and Taylor (3) appears to be infectious and communicable, although a specific causative agent has not been demonstrated. In one of the patients we have studied, portions of lung removed at autopsy were preserved in glycerin, macerated in isotonic saline, and the fluid inoculated intranasally and intracranially into mice, rats, and cotton rats. No lesions were produced.

There has been considerable debate concerning the very existence of alveolar cell tumor, that is, tumor of intra-alveolar origin and growth, independent of the bronchial system. The basis for much of this debate is the controversy over the nature of the cells bordering the alveoli in the lungs of normal adults. Three views are held: first, that alveoli have a continuous epithelial lining; second, that alveoli have a discontinuous epithelial lining; third, that no true lining exists, but that occasional septal cells of mesenchymal origin occur between the

capillaries. At present, the weight of opinion supports the third view. Those who believe in an epithelial alveolar lining readily accept the existence of the tumor and trace it to this epithelium. Those who deny the existence of an alveolar lining discard the possibility of alveolar cell tumors on that basis.

Summarizing the views concerning the specificity of the germ layers, Oppenheimer (4) concluded that it is possible for mesenchymal cells to give rise to tumors with epithelial-like cellular elements. Herbut (5) studied regenerating epithelium lining alveoli in cases of bronchiectasis by serial sections and concluded that the regenerated epithelium was derived from bronchiolar epithelium. The finding of mucin-producing columnar cells in some alveolar cell tumors favors origin from bronchiolar epithelium. Geever, Neubuerger, and Davis (6) and others have shown that epithelial-like lining cells are present in a variety of pathologic conditions, among which are viral pneumonia, lipoid pneumonia, tuberculosis, silicosis, and radiation injury. Bell (7) states that, in any disease which brings about marked thickening of the alveolar septa, the alveolar epithelium may undergo hyperplasia to form a continuous epithelial lining. From observation of transitional stages, he concluded that the epithelium forms locally and does not grow in from the bronchi.

Similar tumors in animals appear to arise in alveolar cells. Grady and Stewart (8) induced multiple pulmonary tumors in mice by the subcutaneous injection of 1, 2, 5, 6-dibenzanthracene and methylcholanthrene. Practically all of these growths arose in the alveoli and not in the bronchi. Cowdry and Marsh (9) studied a disease in sheep called jaagziekte, in which there is pulmonary adenomatosis. They concluded that the proliferated cells arise from alveoli.

The authors agree with many others who have thought that the distribution of the tumor cells in multiple foci lining alveoli, and without demonstrable continuity with bronchiolar epithelium, argues for an alveolar origin of the growth. We believe that the cases described above showed tumors of multicentric origin because (*1*) we were able to demonstrate tumor cells in lymphatics in only 2 cases, (*2*) it seems unlikely that lymphatic spread could reproduce the alveolar pattern in other parts of the lung, and (*3*) the possibility of spread by bronchiolar lumina has not been proved.

Pathologic Anatomy

Two gross forms of this tumor have been described, the multiple nodular and the diffuse. In the former, many tumor nodules, ranging up to approximately 2.0 cm. in diameter, are found more or less evenly distributed over both lungs. The intervening lung tissue sometimes exhibits varying degrees of inflammation, but it may be fairly intact. Four patients in our series exhibited lesions of this type. The diffuse form is characterized by involvement of a lobe or an entire lung on one or both sides. The gross picture simulates lobar pneumonia in the stage of gray hepatization. Case 2 of our series was of this diffuse type.

Microscopically the two forms are identical. The tumor stroma is made up of the alveolar walls which show varying amounts of thickening by fibrous tissue. The alveolar walls are lined by nonciliated cuboidal or columnar cells, frequently

forming papillary protrusions into the alveoli. The cells show varying degrees of anaplasia and hyperchromatism. In some cases many of the cells exhibit bizarre forms. Mitotic figures may be fairly numerous but are usually rare. Many of the cells are seen lying free in alveoli. Mucinous secretion was noted in 3 of our cases.

In approximately half of the reported cases metastases were found. Some authors have used the term pulmonary adenomatosis to designate tumors of this type which showed no metastases. We believe that both the metastasizing and nonmetastasizing forms are essentially similar. It is conceivable that some of the patients failed to develop metastases because of early death from respiratory failure. The short duration of symptoms in some of the patients in this series and in many of those previously reported gives some support to this possibility. Four of our patients exhibited no metastases. One (Case 4) had metastases to the pleura demonstrated at thoracotomy. An autopsy was not performed on this patient so we are unable to state what other metastases may have been present.

Summary of Clinical and Radiologic Data

To encounter 5 cases of this unusual disease in less than one year raises the question of whether this disease is more common than was previously realized or whether this represented a localized "epidemic." There was apparently no contact among these patients, and they came from scattered areas in the city and neighboring parts of the state.

All of the patients reported here were females. Their ages ranged from 57 to 83 years with an average of 72 years. Only one patient in this series was less than 70 years of age.

The disease was chronic but progressive in all 5 patients. Death occurred in an average of fifteen months from the onset of symptoms. The duration of life from the onset of symptoms varied from one to twenty-five months. One of these patients had a family history of cancer of the lung. The principal symptoms were cough, dyspnea, and expectoration of moderate amounts of whitish foamy or mucoid material. Pleuritic chest pain, weight loss, and slight fever were also common complaints. Two patients had orthopnea, one complained of anorexia, and one had had diarrhea. It is interesting to compare those symptoms with those listed by Neubuerger and Geever (1), who gave cough, hemoptysis, cyanosis, chest pain, pleural effusion, and signs of brain metastasis as the cardinal symptoms of this disease. Individual patients in the present series showed all of these signs except those of brain metastasis. Only one patient had definite hemoptysis.

Physical findings in the chest were highly variable. In general, abnormal signs were present bilaterally, although they were not sufficient to suggest as extensive a process as was revealed by the roentgenogram. Cyanosis was definite and marked at some stage in practically all patients. There was little or no clubbing of the fingers. Three of the patients had some associated heart disease, as might be expected in persons in this age group, and the presence of this factor tended to confuse the diagnosis. All of the patients periodically had a low-grade fever with mild tachycardia. The increase in respiratory rate was a striking phenome-

non, especially as a terminal event. These individuals apparently died in respiratory failure with extreme cyanosis, in spite of administration of oxygen. Two patients had a moderate increase in the leukocyte count, 3 had a shift to the left on the differential leukocyte count, and 2 had moderate anemia. The sedimentation rate was found to be elevated in the one patient in which it was determined. Examinations of the sputum were invariably negative for any specific causative organisms. In only one patient was the sputum examined for malignant cells, and in this case the examination was negative. Total serum proteins and albumin-globulin ratios were normal in 3 patients. One patient had a normal electrocardiogram, in another the electrocardiogram showed evidence of myocardial damage manifested by low voltage QRS complexes and slurring of the QRS complexes, with upright T waves. Other laboratory examinations were essentially negative.

Roentgenographic examination of the chest gave definite positive findings in every instance. Infiltration in the lung fields was described in every case, bilateral in all but one. The infiltrations were variously described as diffuse, fibrotic, mottled, nodular, conglomerate, and feathery. Tuberculosis and primary atypical pneumonia were the diagnoses most commonly suggested on the basis of the appearance of the chest roentgenograms. As a rule, tuberculosis could be virtually excluded by repeatedly negative examinations of sputum in the presence of obviously far advanced disease. Generally the process was more chronic, more severe, and more constantly progressive than primary atypical pneumonia. The infiltrations changed little over a long period of observation but pleural effusion was observed to occur in one case.

These patients received a variety of therapeutic measures without apparent benefit from any. Oxygen therapy seemed to be only of temporary value in prolonging life. Intravenous injection of aminophylline seemed to be of some benefit for the severe terminal dyspnea in one patient.

Diagnosis

At the present time a positive diagnosis of alveolar cell tumor can be made only by thoracotomy and biopsy of the lung as was done in Case 3. Cytologic studies of sputum may aid in making the diagnosis, although in one of the cases in this series this study was negative. Woolner and McDonald (10) have reported a case diagnosed through the aid of this method. In our experience, this condition has been mistaken most often for tuberculosis and primary atypical pneumonia. It should be possible to exclude tuberculosis on the basis of repeated negative examinations of sputum, and primary atypical pneumonia could be excluded because of the protracted progressive course. When these conditions have been ruled out, metastatic carcinoma (particularly of the lymphangitic type), Boeck's sarcoid, pulmonary fibrosis, and pneumoconiosis must be considered.

The authors believe that consideration of the usual clinical picture of this disease as exemplified by these cases may lead to its more frequent diagnosis during life. Study of the relationship of this tumor to infection and anoxemia

resulting from alveolar wall fibrosis may open interesting avenues in the study of the etiology of other malignant neoplasms.

Nomenclature

There is great difference of opinion concerning the proper nomenclature of this disease and also concerning the pathologic criteria for its diagnosis. For example, Swan (11), in a recent report, has included only those cases in which the cells lining the alveoli are columnar and contain mucoid droplets. Only 3 of our 5 cases satisfy this criterion. Cases 1 and 5 did not show mucous secretion. We feel, however, that it is unwise to make mucous secretion an essential feature of this diagnosis.

Whatever position one may take concerning nomenclature, the fact remains that the cases reported here, as well as those previously reported by others, should be differentiated from more common types of pulmonary carcinoma for the following reasons: (*1*) They are diffuse or multicentric rather than localized in origin; (*2*) there is no discoverable primary focus; (*3*) there is no evidence of origin from bronchial epithelium; (*4*) the malignant cells line the alveoli; (*5*) death occurs from respiratory failure usually before metastasis has occurred; (*6*) in both involved and uninvolved areas there is fibrous thickening of alveolar walls, suggesting a preceding, organizing, interstitial pneumonia; (*7*) the preponderance in males, characteristic of other types of carcinoma of the lung, is not seen; and (*8*) the problem of diagnosis and treatment is quite different from that involved in other types of pulmonary malignancy.

Of the various names proposed for this condition, including pulmonary adenomatosis and alveolar carcinoma, the term alveolar cell tumor seems preferable, since it is noncommital concerning the germ layer of origin and includes both metastasizing and non-metastasizing tumors of this type.

Summary

Five cases of alveolar cell tumor of the lung are presented, and the clinical and pathologic features discussed. All of the cases in this series occurred in females. The average age was 72 years and the average duration of life from the onset of symptoms was 15 months.

The principal symptoms were dyspnea, cough, and expectoration of moderate amounts of whitish foamy or mucoid material, pleuritic chest pain, and weight loss. The physical findings included cyanosis, tachypnea, and low-grade fever. Alterations in breath sounds or percussion note, together with rales on both sides of the chest, were usually noted. Laboratory studies revealed a mild anemia and an elevated leukocyte count with a shift to the left in the differential count in approximately half of the cases. Examinations of sputum were entirely negative, but in only one case was the sputum examined for malignant cells.

Roentgenographic examination of the chest seemed in retrospect to be the most valuable diagnostic measure in this disease. The films were most frequently misinterpreted as tuberculosis or primary atypical pneumonia, the former being ruled out by the absence of tubercle bacilli in the sputum and the latter by the protracted downhill course.

At present the only method of exact diagnosis of alveolar cell tumor is by

thoracotomy and removal of a biopsy specimen for microscopic examination. Presumptive diagnosis may be made on the basis of cytologic study of the sputum.

Sumario

Tumor Alveolocelular del Pulmón

Al presentar 5 casos de tumor alveolocelular del pulmón, discútense las características clínicas y patológicas. Todos los casos de esta serie fueron en mujeres. La edad promediaba 72 años y la duración de los síntomas desde la iniciación hasta la muerte promedió quince meses.

Los principales síntomas consistieron en disnea, tos, expectoración de cantidades moderadas de una sustancia blancuzca espumosa o mucoidea, dolor pleurítico en el tórax y pérdida de peso. Los hallazgos físicos comprendieron cianosis, taquipnea y febrícula. Por lo general, notóse alteración de los ruidos respiratorios o del timbre de percusión, con algunos estertores en ambos lados del tórax. Los estudios de laboratorio indicaron existencia de anemia leve y de hiperleucocitosis con desviación hacia la izquierda aproximadamente en la mitad de los casos. Los exámenes del esputo resultaron absolutamente negativos, pero sólo en un case se buscaron células malignas en el mismo.

El examen radiográfico del tórax pareció restrospectivamente constituir la providencia más valiosa de diagnóstico para dicho estado. Las radiografías fueron con suma frecuencia interpretadas erróneamente como tuberculosis o neumonía atípica de etiología viral, excluyendo la primera la ausencia de bacilos tuberculosos en el esputo y la segunda la prolongada evolución y agravación.

Por ahora, el único método para hacer el diagnóstico acertado de dicho estado es por medio de la toracotomía y la obtención de un ejemplar de biopsia. Puede hacerse el diagnóstico presuntivo a base del estudio citológico del esputo.

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AN EVALUATION OF CERTAIN DOSAGE FORMS OF PARA-AMINOSALICYLIC ACID (PAS)[1]

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INTRODUCTION

The use of para-aminosalicylic acid (PAS) in the therapy of tuberculosis represents a step forward in the chemotherapy of this disease. Acceptance of this relatively new agent has been based upon its inhibitory effects on tubercle bacilli (1, 2, 3), on the results of treatment of experimentally produced tuberculosis in laboratory animals (4), and on the confirmation of the initial favorable clinical reports (5, 6) by an increasing number of investigators. An excellent review of the extensive literature on the use of para-aminosalicylic acid in tuberculosis has recently been published (7). A major difficulty in the clinical application of PAS has been the almost universal observation that doses in excess of 8 to 12 gm. per day induce nausea and vomiting in a majority of patients. These symptoms make it nearly impossible to employ the daily doses of 20 to 24 gm. that have been recommended (6, 8). Attention has been called to the fact that the physical characteristics of the form in which the drug is administered may have a bearing on this point, the hydrochloride being more irritating than the free base and the free base being more irritating than the sodium salt of PAS.

Data on the plasma concentrations of PAS resulting from various treatment schedules should make possible more purposeful use of the drug and more accurate interpretations of clinical results observed following various regimens of therapy. Little information is available to provide correlation of the clinical course of tuberculosis treated with PAS and the plasma concentrations of PAS achieved with the particular dosage employed. It seems reasonable to strive for plasma concentrations of PAS in excess of the *in vitro* sensitivity of the tubercle bacillus, although the degree to which it is desirable to achieve high PAS concentrations in the plasma and the best means of attaining them have not been made clear. Attainment of higher plasma concentrations of PAS by the use of the free acid of PAS is difficult because of the gastrointestinal symptoms caused by large doses of the drug and, although the sodium salt of PAS is better tolerated, the observation has been made that the drug administered in this form is more rapidly excreted (9). In view of the lack of comparative data, the present study was undertaken to compare the plasma concentrations of PAS resulting from administration of the drug in the form of the free acid with those obtained with the sodium salt.

Methods of Study

The patients studied in this investigation had active pulmonary tuberculosis but were otherwise in good physical condition. Microscopic examinations of the urine sediment,

[1] From the Philadelphia General Hospital, Philadelphia, Pennsylvania.

Fishberg concentration tests, and phenolsulfonphthalein excretion tests were performed to determine freedom from obvious renal dysfunction. PAS was administered orally in all instances, and plasma concentrations of PAS were determined by the method of Way (10). For the purposes of study the patients were divided into two groups, to one of which were administered single doses and the other, repeated doses of PAS.

RESULTS

Single doses: Oral doses of 2, 4, 6, and 8 gm. of the sodium salt of PAS in aqueous solution[2] were administered as single doses to groups of 5, 12, 5, and 6 patients, respectively. A group of 9 patients received a single dose of 4 gm. of the free acid in tablet form[3]. Blood samples for determinations of plasma PAS were obtained at one-half, two, four, six, and eight hours following the administration of each test dose of PAS. In this series of patients receiving single oral doses of drug, 185 PAS plasma determinations were performed. The values obtained following single doses of the sodium salt are shown in figure 1. In figure 2 are shown the plasma concentrations resulting from equivalent doses of the free acid and the sodium salt of PAS.

The majority of patients in this series tolerated single doses of 8 gm. of the sodium salt without developing irritability of the gastrointestinal tract. Only an exceptional patient, however, could tolerate more than 4 gm. of the free acid as a single dose. The plasma concentrations observed after 4 gm. of PAS administered in the two forms (figure 2) clearly indicate that the gastrointestinal disturbance could not be correlated with the plasma concentrations of the drug.

Repeated doses: During a series of study periods (none less than forty-eight hours), a group of 6 patients received: (a) 2 gm. of free acid every three hours, (b) 3 gm. of free acid every three hours, (c) 2 gm. of sodium PAS every three hours, and (d) 3 gm. of sodium PAS every three hours. Blood samples were obtained one-half, one and one-half, and three hours after the test dose of PAS, and plasma concentrations were determined. A total of 179 determinations were done during a period of study representing 209 patient-days of PAS therapy. The results are recorded in figure 3.

Most patients can tolerate between 8 and 12 gm. of PAS in the form of the free acid when administered in divided doses, but the range of dosage with sodium salt has been 12 to 24 gm. when administered to the same patients. While there may be individual exceptions to these arbitrary figures, the majority of the patients were able to tolerate 2 to 5 gm. per day more PAS in the form of the sodium salt than when the free acid was administered.

Renal excretion: Urinary recoveries of PAS over periods of six hours after single doses and over the twenty-four-hour period when repeated doses were administered are presented in figure 4. It is generally stated that from 40 to 60

[2] The authors are indebted to Sharp & Dohme, Inc. for supplies of Propasa, effervescent tablets of PAS. Each tablet contains 1 gm. of PAS as the free acid and a quantity of sodium bicarbonate sufficient to convert the acid to the sodium salt when the tablet is added to 15 to 30 ml. of water shortly before administration.

[3] Pamisyl tablets of PAS, each containing 0.3 gm. of PAS, were generously supplied by Parke, Davis & Company.

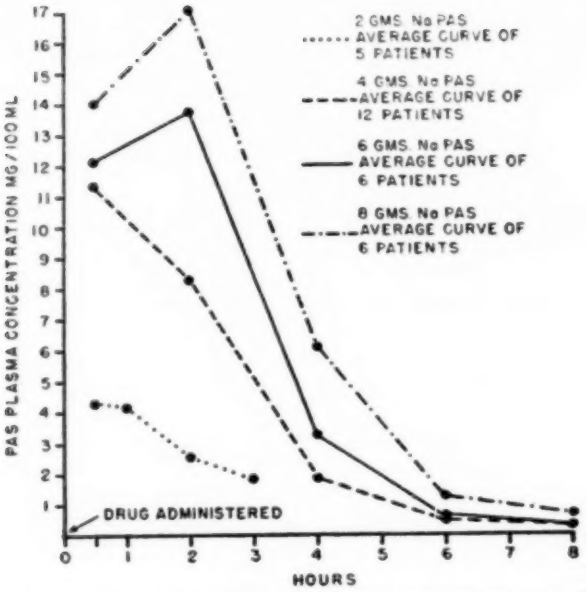

FIG. 1. PAS plasma concentrations after single doses of sodium salt of PAS

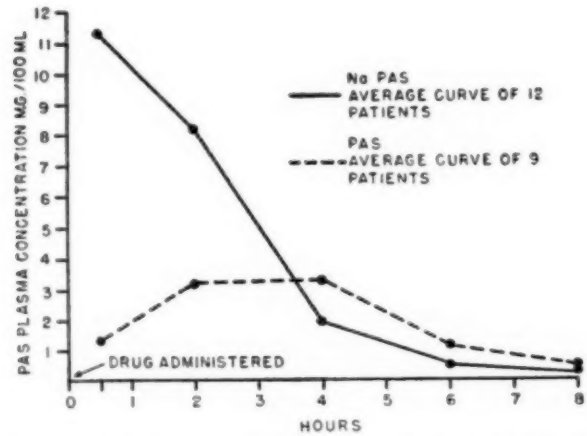

FIG. 2. Comparison of 4 gm. doses of PAS administered as the free acid and the sodium salt

per cent of an orally administered dose of PAS is recovered in the urine. The *average* recoveries as observed in these experiments were in agreement (figure 4). Attention is called, however, to the recoveries as observed in one patient (W. W.)

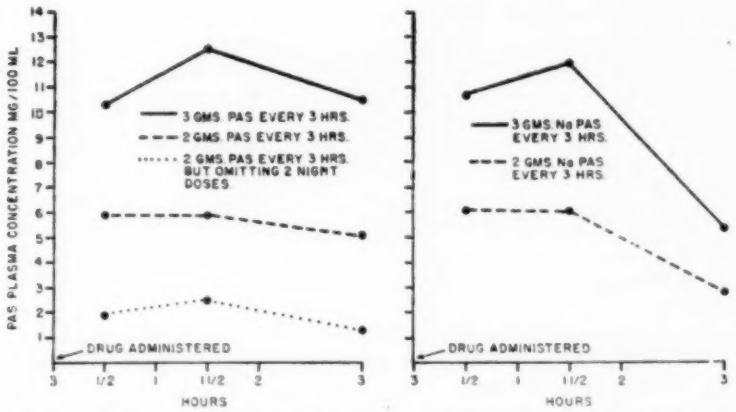
PAS PLASMA CONCENTRATION MG/100 ML.
3 GMS. PAS EVERY 3 HRS.
2 GMS. PAS EVERY 3 HRS.
2 GMS. PAS EVERY 3 HRS. BUT OMITTING 2 NIGHT DOSES
DRUG ADMINISTERED
HOURS
3 GMS. No PAS EVERY 3 HRS.
2 GMS. No PAS EVERY 3 HRS.
DRUG ADMINISTERED
HOURS

FIG. 3. PAS plasma concentration following administration of free base and sodium salt of PAS in continuous dosage.

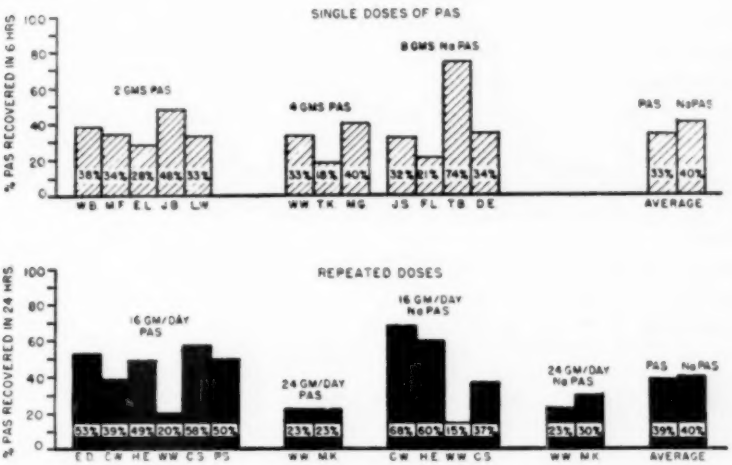

FIG. 4. PAS urinary recoveries

during four twenty-four-hour periods, 20, 23, 15, and 23 per cent, respectively; and in patient M. K., on two occasions, 23 and 30 per cent. These recoveries, repeatedly observed in the same persons, stand in sharp contrast to recoveries of

58 and 68 per cent in other patients. It is our belief that the metabolism of PAS by different individuals may be strikingly different, and this variability emphasizes the need for fuller understanding of the metabolism of PAS in the human body. The degree to which individual handling of the drug may influence its therapeutic effectiveness is unknown, but it seems to be an important question.

DISCUSSION

The optimal dosage of PAS in tuberculosis therapy has not been established. It is probable that individualization of therapy is desirable in view of the variability in: (a) the sensitivity of strains of tubercle bacilli, (b) the type of tuberculous lesion under treatment, (c) the rate of development of resistance to PAS, and (d) the quantity of PAS that can be tolerated without untoward symptoms. Although some strains of tubercle bacilli not previously exposed to the effects of PAS are inhibited by concentrations of PAS as low as 0.015 mg. per 100 ml., as much as 1.53 mg. per 100 ml. has been required to inhibit the growth of all strains tested (2). Thus, it seems likely that the plasma concentrations ranging from 2 to 7 mg. per 100 ml. that are attained when 10 to 14 gm. of PAS are administered daily are capable of inhibiting the growth of tubercle bacilli (12), (figure 3). The likelihood that this assumption is correct is increased by the fact that dilutions of blood plasma as high as 1:50 obtained at intervals up to four hours after the oral administration of 2 and 4 gm. of PAS are capable of inhibiting the growth of tubercle bacilli (13). Despite these demonstrations that tubercle bacilli are sensitive to low concentrations of PAS such as are attained by the doses of PAS commonly prescribed, it must be emphasized that plasma concentrations are only an indirect indication of the concentrations that obtain at the actual sites of tuberculous infection.

The therapeutic index of PAS is high and no serious complications have been reported from its use in man. The quantity that can be administered orally is determined by the amount of drug a patient is able to tolerate without gastrointestinal symptoms. The symptoms of anorexia, nausea, vomiting, and diarrhea are probably attributable in large part to the physical properties of the form of PAS that is employed. That PAS produces symptoms by reason of local gastrointestinal irritation is substantiated by studies in which massive doses of PAS have been administered intravenously for periods up to six weeks, without the development of gastrointestinal symptoms even though plasma concentrations reached 40 mg. per 100 ml. (15). These observations are in accord with our own findings, namely, that there was no correlation between plasma concentration of PAS and untoward gastrointestinal symptoms.

Aside from the decreased irritability of the gastrointestinal tract when the sodium salt of PAS was employed, the sodium salt was both more rapidly absorbed and more rapidly excreted (figures 2 and 3). There was a progressive increase in the peak concentration of PAS obtained in the plasma with increasing doses of the sodium salt, but there was not a commensurate prolongation of detectable concentrations in the plasma (figure 1). The difference in pattern of the plasma concentrations of PAS when the free acid and the sodium salt are

administered is great when single doses are compared (figure 2), but when repeated doses are administered there is little difference in the resulting plasma concentrations (figure 3). The similarity of the plasma concentrations parallels the urinary recoveries of PAS which are approximately equal whether the sodium salt or the free acid is administered (figure 4). The curves in figure 3 represent the averages of the same 6 patients on the different dosage schedules and it should be stated that great difficulty was encountered in finding 6 patients who were able to tolerate 24 gm. per day of the free acid for the purpose of making these comparisons. Another point of interest is the fact that all blood samples were drawn after the 9 a.m. medication and it is clear that the omission of the 3 a.m. and 6 a.m. doses of drug is reflected in the much lower plasma concentrations observed the following morning.

It seems reasonable to suggest that PAS distributes itself in the tissues by diffusion and that, therefore, an increase in PAS plasma concentrations will give rise to relative increases in the tissue concentration of PAS. The emergence of PAS-resistant strains of tubercle bacilli (14) indicates the desirability of attaining maximal plasma concentrations of the chemotherapeutic agent from the beginning of therapy. Perhaps by the attainment of high plasma concentrations the tissue concentrations of PAS will be increased, the therapeutic effectiveness may be increased, and the likelihood of the emergence of PAS-resistant strains of organisms lessened.

Attainment of higher plasma concentrations has been limited by the fact that the free acid cannot be administered in doses larger than 8 to 12 gm. per day and, although the sodium salt gives rise to higher plasma concentrations, the drug is excreted rapidly. Thus, there would appear to be a place in therapy for an agent capable of increasing plasma concentrations of PAS by retarding the rate of its elimination. It has been observed that carinamide is capable of increasing PAS plasma concentrations in the plasma by two- to four-fold (16, 17, 18). Unfortunately, this observation is of little practical importance, since the large dose of carinamide required to produce this effect (24 gm. per day) produces nausea and vomiting in approximately 15 per cent of patients (19). Another compound, *p*-(di-n-propylsulfamyl)-benzoic acid, Benemid[4], that appears to be nontoxic and orally effective has been found to increase plasma concentrations of PAS by two- to four-fold when administered in a daily dose of 2 gm. (19, 20). It seems practical, therefore, to attain high plasma concentrations of PAS by the combined use of sodium PAS and Benemid and to explore the therapeutic possibilities of the resulting high plasma concentrations of PAS.

SUMMARY

Patients with tuberculosis were given single doses of PAS in the form of the sodium salt and the free acid. Plasma concentrations of PAS resulting from the administration of 2, 4, 6, and 8 gm. of sodium salt are presented and a comparison made in the same patients between the concentrations resulting from 4 gm.

[4] Benemid is the Sharp & Dohme, Inc. trademark for *p*-(di-n-propylsulfamyl)-benzoic acid. This compound has been assigned tentatively the chemical designation, "probenecid."

of the sodium salt and 4 gm. of the free acid. The plasma concentrations following repeated doses of 2 and 3 gm. of both the sodium salt and the free acid of PAS have also been compared. Whereas the sodium salt gives rise initially to higher plasma concentrations, the concentrations fall faster than those after the administration of the free acid. From the standpoint of maintaining plasma concentrations of PAS, the omission of the night doses of PAS is disadvantageous. The urinary recoveries of free acid and the sodium salt of PAS are approximately equal. The sodium salt of PAS has the advantage over the free acid of giving higher plasma concentrations and causing fewer gastrointestinal symptoms.

SUMARIO

Justipreciación de Ciertas Formas Posológicas del Acido Para-Amino-salicílico (PAS)

Dosis aisladas de PAS, en forma de la sal sódica y del ácido libre, fueron administradas a tuberculosos. Preséntanse las concentraciones de PAS obtenidas en el plasma con la administración de 2, 4, 6 y 8 gm. de la sal sódica, y se comparan las debidas a 4 gm. de la sal sódica con las obtenidas con la administración a los mismos enfermos de 4 gm. del ácido libre. Comparáronse las concentraciones plasmáticas consecutivas a dosis repetidas de 2 y 3 gm. tanto de la sal sódica como del ácido libre de PAS. Mientras que la sal sódica evoca inicialmente concentraciones más elevadas en el plasma, éstas descienden con mayor rapidez que las consecutivas a la administración del ácido libre. En lo tocante a mantener concentraciones de PAS en el plasma, la omisión de las dosis nocturnas resulta desventajosa. Las cantidades del ácido libre y de la sal sódica del PAS obtenidas de la orina son aproximademente iguales. La sal sódica del PAS posee sobre el ácido libre la ventaja de crear concentraciones plasmáticas más altas y de ser mejor tolerada con respecto a provocar síntomas gastrointestinales.

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PROMIZOLE: FACTORS DETERMINING ADEQUATE DOSAGE[1,2,3,4]

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INTRODUCTION

Investigations of the effects of various sulfone derivatives in the chemotherapy of tuberculosis were begun in 1938. Certain of these agents, 4,4′-diaminodiphenylsulfone, and its derivatives, sodium *p,p′*-diaminodiphenylsulfone-N,N′-didextrose sulfonate (Promin) and disodium formaldehyde sulfoxylate diaminodiphenylsulfone (Diasone), were found to exert a definitely favorable influence on the course of experimental tuberculosis in the guinea pig in a significant percentage of trials (1–8). The toxicity of these compounds, however, particularly those of hematoxic nature, and the small range between therapeutic and toxic dosage soon limited their use in human tuberculosis (9, 10, 11). With the synthesis of 4,2′-diamino-diphenyl-5′-thiazolesulfone (Promizole) in 1942 by Bambas (12), a sulfone derivative was made available which exhibited minimal toxity for humans and which had therapeutic effects upon guinea pig tuberculosis comparable to those obtained with Promin and Diasone (3).

In 1944 Promizole was used on the Children's Medical Service of Bellevue Hospital in the treatment of 5 children with miliary tuberculosis (15, 17). The apparent cure of 3 of these children gave evidence of the effectiveness of the drug in human tuberculosis. Promizole was used alone until streptomycin was introduced, at which time the two agents were used in the treatment of all cases of miliary tuberculosis and tuberculous meningitis as well as in selected cases of other types of tuberculous infection. The clinical results obtained by Lincoln and her associates are reported elsewhere (16, 17, 18).

In the original report on the clinical administration of Promizole by Hinshaw, Feldman, and Pfuetze (14), it was stated that "there are inconsistencies in the results obtained in studies on blood concentration which we have not yet explained to our satisfaction." In the attempt to achieve Promizole blood levels of 2 to 3 mg. per 100 cc., as suggested by the animal experiments of Feldman, Hinshaw, and Mann (13), these inconsistencies soon became apparent to us as well. The marked variability observed in the relationship between the dosage administered and the blood levels obtained appeared to be independent of age, sex, weight, and type of disease. From the numerous inquiries we have received it is evident that these discrepancies are causing concern among other groups working

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with the drug. It seemed advisable, therefore, to present at this time the results of certain investigations on the pharmacologic properties of Promizole which have a bearing on this problem.

Materials and Methods

Promizole, the trade name for 4,2′-diamino-diphenyl-5′-thiazolesulfone, has a molecular weight of 255. It is soluble in water to the extent of 30 to 40 mg. per 100 cc. at pH 6.5, temperature of 28° to 30° C. It is readily soluble in dilute acids, acetone and 70 per cent ethyl alcohol, while moderately soluble in absolute alcohol, ethyl acetate, and ether. Promizole is supplied in tablets of 0.5 gm.

The drug was administered on the ward of the Childrens' Chest Service of Bellevue Hospital to patients who had tuberculous meningitis, miliary and certain other forms of progressive tuberculous disease. The ages varied from six months to twelve years. In some instances the drug was administered to nontuberculous convalescent children. The dosages employed are noted below.

The drug was administered in tablet form to the older children, while for the infants the tablets were crushed and suspended in water to which sugar was added as flavoring. Specimens of blood were taken regularly at an interval of two to three hours after the administration of Promizole. Promizole concentrations in blood, urine, and stool were determined by the method of Bratton and Marshall (19).

Method of Determination of Promizole in Body Fluids

Reagents: Trichloroacetic acid—15 per cent. Sodium nitrite—0.1 per cent (prepared freshly). Ammonium sulfamate—0.5 per cent N (I Naphthyl) ethylene-diamine dihydrochloride (Eastman Kodak Co.)—0.1 per cent in aqueous solution stable to approximately two weeks when kept in dark bottle.

Standard: 100 mg. *dried* crystalline Promizole were dissolved in 100 cc. distilled water to which 1 cc. concentrated hydrochloric acid had been added. (The drug administered for medications cannot be used as a substitute for crystalline Promizole.) Heating slightly aided solution. When cool, the solution was diluted to one liter. This solution was stable when stored in a refrigerator. A *working* standard was prepared by diluting 10 cc. stock standard to 100 cc. with distilled water.

Method: Free Promizole: To 7.5 cc. distilled water were added 0.5 cc. of plasma and 2 cc. of 15 per cent trichloroacetic acid, allowed to stand ten minutes, and then filtered.

To 5 cc. of filtrate was added 0.5 ml. of sodium nitrite, mixed well, and allowed to stand three minutes; 0.5 ml. of 0.5 per cent ammonium sulfamate was added, mixed well, and allowed to stand two minutes. Finally 0.5 ml. of N (I Naphthyl) ethylene-diamine dihydrochloride was added as the color indicator.

A test reading for comparison was prepared by using 1 cc. of the dilute Promizole standard and adding to it 1 cc. of 15 per cent trichloroacetic acid and 3 cc. of water. It was then treated in the same manner as the plasma filtrates. A suitable concentration was .01 mg. per cc.

A reagent blank was prepared by adding 1 cc. of 15 per cent trichloroacetic acid to 4 cc. of water and treated as the plasma filtrates. The solutions were then read in a Klett-Somerson photoelectric colorimeter against the reagent blank set at zero, using a filter transmitting 540 microns.

Total Promizole (free and acetylated): 5 cc. of filtrate were placed in a boiling water bath for one hour. After cooling, the water lost by evaporation was replaced and filtrate was treated as for free Promizole.

Cerebrospinal and pleural fluids were analyzed in the same manner as plasma. If the colorimeter readings were too low, the amount of fluid used was increased.

Stool: A total 24-hour specimen was mixed thoroughly in about 200 cc. of 95 per cent alcohol. One cc. of concentrated hydrochloric acid was added and the mixture was diluted to 300 cc. with 95 per cent alcohol; 10 cc. of the mixture were withdrawn and centrifuged at high speed. The supernatant fluid was suitably diluted 1:10, 1:25, 1:50, 1:100 and treated in the same manner as for blood plasma determinations.

Urine: The specimen was suitably diluted with distilled water as described above and treated as for the determination of blood plasma level.

RESULTS

In table 1 are listed a random series of determinations of concentrations of Promizole in the blood of patients with tuberculosis under treatment with this

TABLE 1

Concentrations of Promizole in the Blood of Patients Receiving Various Oral Dosages

PATIENT	WEIGHT	AGE	DAILY DOSE OF PROMIZOLE		AVERAGE CONCENTRATION IN BLOOD	DIAGNOSIS
			Total gm.	Gm. per kg.		
	kilograms	*years*			*mg. per 100 cc.*	
A.	11.5	1 1/2	0.5	0.04	3.96	Miliary TB
W. S.	12.5	3	0.5	0.04	4.48	Miliary TB, Potts disease
K.	14.5	5	1.0	0.07	3.84	Tuberculous meningitis
M.	10.9	1/2	2.0	0.18	2.70	Progressive primary TB with cavitation
R.	13.7	3	3.0	0.22	0.73	Miliary
A. M.	9.1	1/2	4.0	0.44	1.0	Miliary TB; meningitis
V. M.	14.1	1 1/2	4.0	0.28	1.03	Progressive primary TB with cavitation
R. M.	10.1	2 1/2	4.0	0.37	1.62	Progressive primary TB with cavitation
R. C.	12.0	1 1/2	4.0	0.37	1.35	Meningitis
M. P.	25.2	6	6.0	0.25	1.13	Meningitis and calcifications in lung
C. M.	37.3	13	6.0	0.16	1.83	Chronic pulmonary TB
M.	12.9	3 1/2	6.0	0.47	1.34	Meningitis
B. P.	16.6	4	8.0	0.5	1.58	Meningitis
R. K.	27.3	8	8.0	0.29	0.93	Chronic pulmonary TB
M. M.	22.0	5	8.0	0.36	1.48	Meningitis and calcifications in lung
P.	30.5	5	8.0	0.26	0.87	Meningitis

drug. Data such as these serve to emphasize the marked variations among individuals in the concentrations of Promizole in the blood in relation to the oral dosage administered.

ABSORPTION OF PROMIZOLE FROM THE GASTROINTESTINAL TRACT

Four children under treatment with Promizole for tuberculosis were taken off the drug until none could be detected in blood, urine, or stool. Each of the children was then given 0.08 gm. of Promizole per kg. of body weight in a single

dose. The same dose was administered to 3 normal children who had never before received the drug. All stools were collected until Promizole could no longer be detected, and the recovery of the Promizole determined. The results are shown in table 2. It may be seen that in both normal subjects and tuberculous patients absorption of the drug from the gastrointestinal tract was fairly complete. Despite the limited solubility of the drug, absorption after oral administration ranged from 86 per cent to 98.6 per cent.

TABLE 2

Absorption of Promizole from Gastrointestinal Tract

SUBJECT	ORAL DOSE (GM.)	RECOVERED IN STOOL (GM.)	PERCENTAGE OF DOSE ABSORBED
Patients with tuberculosis:			
W. S.	0.75	.069	64
R. K.	2.0	.234	88
O. V.	1.5	.115	92
R. A.	1.0	.138	86
Normal children:			
D. O.	3.5	.275	86
W. P.	3.25	.335	90
V. H.	3.5	.051	98.6

Similar doses of Promizole, suspended in acacia, were given to 2 patients by retention enema. No Promizole was detectable in specimens of blood taken subsequently, indicating that the drug is not absorbed from the lower bowel.

CONCENTRATIONS OF PROMIZOLE IN THE BLOOD AFTER ORAL ADMINISTRATION

Single Doses

As mentioned previously, marked variability was encountered in the dose of Promizole required to attain concentrations in the blood of 2 to 3 mg. per 100 cc. To investigate this phenomenon, the concentrations in the blood levels were studied under a variety of conditions.

In figure 1 are presented observations of the concentrations of Promizole in the blood of healthy, nontuberculous children given varying amounts of Promizole in a single dose. It may be seen that no predictable relationship exists between the amount of drug administered, the peak concentrations attained in the blood, and the concentration persisting at the end of eight hours. In general, the highest concentration peak level was found two to four hours following administration of the drug.

In figure 2 are graphically presented the blood concentrations in the 4 tuberculous children mentioned above, each of whom received a single dose of Promizole, 0.08 gm. per kg. These variations demonstrate clearly the tremendous variation in blood concentration obtained after comparable dosage and the com-

plete lack of correlation between dose and blood concentration. At the end of twenty-four hours, patients R. A. and W. S. had blood concentrations which

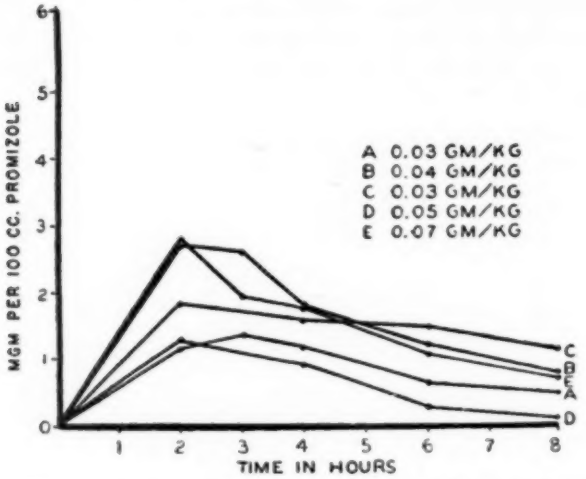

FIG. 1. Blood concentrations of Promizole in normal children on varying doses

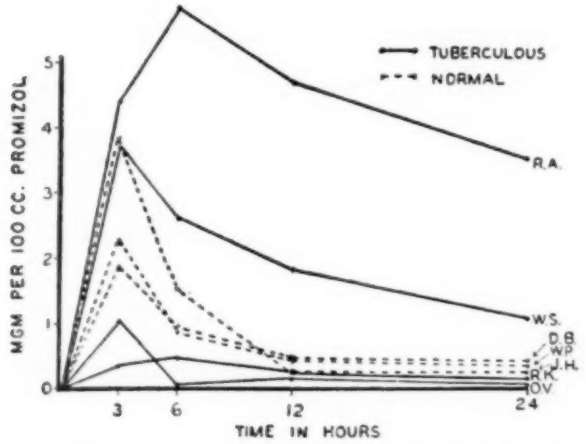

FIG. 2. Blood concentrations on 4 children with tuberculosis receiving 0.08 gm. per kg. in a single dose as compared with 3 normal children.

were higher than the maximum attained by the other 2 patients at any time during the entire twenty-four-hour period. In addition, the latter 2 patients (R. K. and O. V.) at no time attained blood concentrations considered to be therapeu-

tically optimal, while W. S. maintained a desirable concentration for twelve hours, and R. A. for twenty-four hours, following a single dose. It should be emphasized that these patients had been maintained on Promizole for long periods of time prior to the present experiment, so that these curves may not be considered comparable to those of normal children, due to the possibility of varying amounts of tissue saturation in the former. This comparison may be seen in figure 2 which also illustrates the values obtained in 3 normal children also given 0.08 gm. per kg. of Promizole in single doses.

Repeated Doses

In figure 3 are shown concentrations of Promizole in the blood of 5 tuberculous children receiving maintenance doses of Promizole every five hours designed

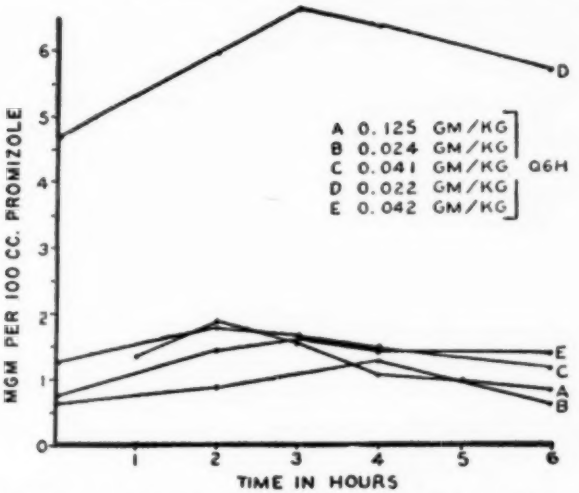

FIG. 3. Promizole blood concentrations in patients with tuberculosis maintained on varying doses given every six hours.

to achieve blood concentrations of 2 to 3 mg. per 100 cc., the drug being administered at five hourly intervals. The curves shown represent the values obtained following one-fourth of the daily dose. It may be seen that patient A, while receiving the highest dose, attained the lowest peak blood concentration. In contrast, patient B, who received the lowest dose, reached and maintained the highest blood concentration of all 5 patients. Moreover, even at six hours, in patient D the concentration of Promizole in the blood was much higher than the peak attained in any of the other 4 children.

In figure 4 are shown graphs of the determinations made in 6 tuberculous children maintained on varying daily amounts of Promizole divided into two doses given at twelve-hour intervals. It is again evident that certain of the patients (D. and F.) were able to maintain high blood concentrations on very

small doses for as long as twelve hours following a dose. It is of interest that these children demonstrate a fairly flat curve for the twelve-hour period and exhibit a negligible rise following the next dose of the drug. In contrast, those children

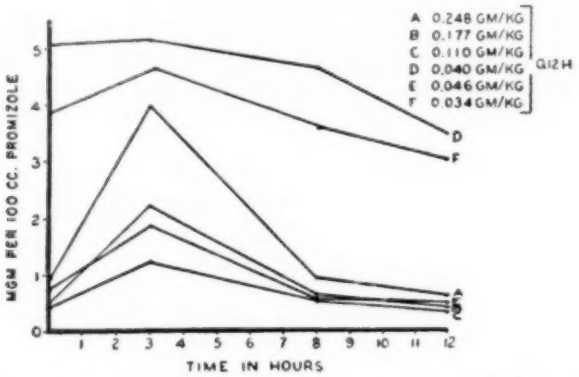

FIG. 4. Promizole blood concentrations in patients with tuberculosis maintained on varying doses given every twelve hours.

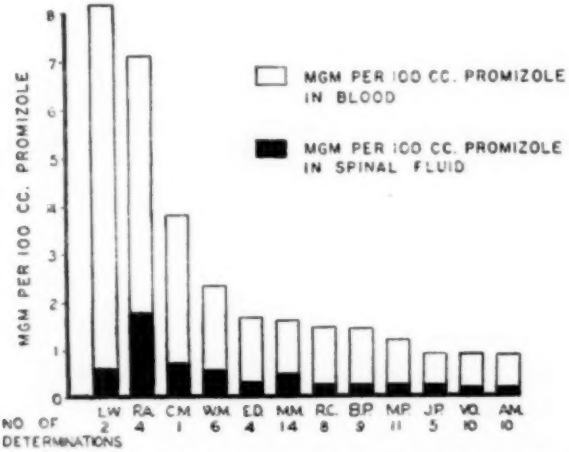

FIG. 5. Cerebrospinal fluid and blood Promizole concentrations in tuberculous meningitis.

requiring larger doses to attain concentrations in the therapeutic range exhibit a more definite rise following the dose but maintain adequate levels for only short intervals.

DISTRIBUTION OF PROMIZOLE IN OTHER BODY FLUIDS

Cerebrospinal Fluid

Simultaneous blood and cerebrospinal fluid concentrations were determined in 12 patients with tuberculous meningitis. The number of determinations per patient ranged from 1 to 14. Averages of these determinations are shown in figure 5. The concentrations in the cerebrospinal fluid range from 18 to 24 per cent of those in the blood. Only in the 2 children with the very high blood concentrations of 8.16 and 7.03 mg. per 100 cc., respectively, were cerebrospinal fluid concentrations obtained which ordinarily would be considered therapeutically effective.

Pleural Fluid

Simultaneous blood and pleural fluid Promizole concentrations were determined on 2 children with tuberculous pleural effusion three hours after the single administration of 1 gm. orally. The results are shown in table 3. In one child

TABLE 3

Concentration of Promizole in Pleural Fluid

PATIENT	PROMIZOLE GIVEN	PROMIZOLE CONCENTRATION MG. PER 100 CC.		
		Blood	Pleural Fluid	Spinal Fluid
I. L.	1 gm.	0.88	0.42	—
S. F.	1 gm.	5.73	5.16	1.72
W. A.	1 gm.	—	1.39	—

(S. F.), almost equally high concentrations were present in both blood and pleural fluid. In another child a low concentration in the blood was associated with a lower concentration in pleural fluid, approximately 50 per cent of that in the blood.

CONJUGATION OF PROMIZOLE IN BLOOD

Free and total Promizole concentrations were determined in the blood of 9 patients, with the results shown in figure 6. The amount of the drug conjugated ranged from 0 to 47.2 per cent of the total Promizole in the blood. In 6 of these patients, however, the conjugated form was less than 10 per cent of the total Promizole, and in 2 patients it was less than 20 per cent. In only one was more than 40 per cent conjugation demonstrated.

EXCRETION OF PROMIZOLE IN THE URINE

The daily urinary excretion of both free and conjugated Promizole was measured in 6 patients who had been maintained on Promizole for long periods of time. The recovery of Promizole in the urine in twenty-four hours, compared with the total daily intake, is shown in figure 7. The average blood concentrations in these patients are indicated in the same figure. It may be seen that the percentage recovery in the urine ranged from 42 to 86 per cent of daily intake.

The recovery in the urine, however, was in no way proportionate to the daily dose. Moreover, differences in the average blood concentration of these patients were apparently not a function of urinary excretion of the drug.

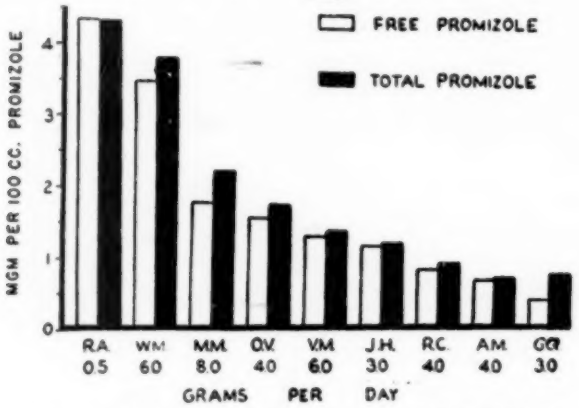

FIG. 6. Concentration of free and total Promizole in blood

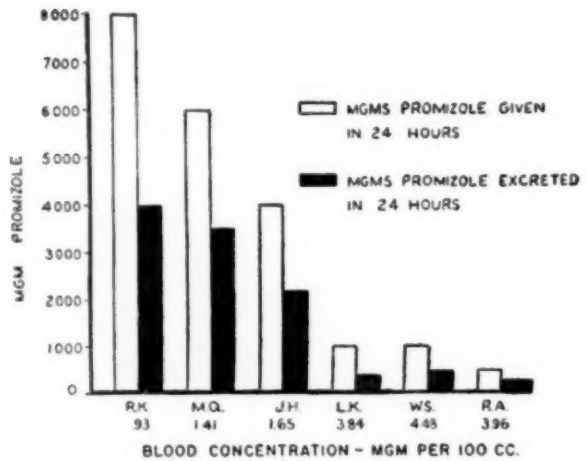

FIG. 7. Relationship between daily intake and urinary excretion of patients maintained on Promizole.

In contrast to these findings are the results obtained in 4 children who were taken off Promizole until none could be detected in the blood or urine and who were given 0.08 gm. per kg. of Promizole in a single dose. As was shown in table 2, these children exhibited almost complete absorption of the drug from the

gastrointestinal tract. The total urinary recovery of Promizole in these patients varied greatly, ranging from 17 to 64 per cent of the administered dose (table 4). When the results of urinary excretion are compared with the blood concentrations obtained in these same patients (figure 2), it may be seen that the 2 patients in whom only very low blood concentrations were attained excreted only 17 per cent and 23 per cent, respectively, of ingested Promizole. One of the patients with high blood concentrations excreted 64 per cent of the ingested drug in the urine. The other, however, excreted only 33 per cent. When these patients

TABLE 4

Recovery of Promizole in Urine

SUBJECT	PEAK BLOOD CONCENTRATIONS AFTER 0.08 GM. PER KG. OF PROMIZOLE IN SINGLE ORAL DOSE	PERCENTAGE OF SINGLE DOSE RECOVERED IN URINE	AVERAGE PEAK OF BLOOD CONCENTRATION ON MAINTENANCE DOSES	PERCENTAGE RECOVERED IN URINE OF PATIENTS ON MAINTENANCE DOSAGE
Patients with tuberculosis:				
W. S.	3.64	61	4.48	50
R. A.	6.35	30	3.96	58
O. V.	0.47	16	1.25	54
R. K.	1.06	20	0.93	54
Normal children:				
W. P.	2.24	64	—	—
J. H.	1.89	82	—	—
D. O.	3.82	83	—	—

TABLE 5

Conjugation of Promizole in the Urine

SUBJECT	FREE PROMIZOLE	TOTAL PROMIZOLE	URINE VOLUME	PER CENT OF TOTAL CONJUGATED
	mg.	mg.		
W. H.	2,115	2,495	545	15.2
M. Q.	3,484	4,190	750	16.8
R. A.	290	310	465	0
R. K.	3,900	4,000	790	2.5
O. V.	2,030	2,128	615	4.6
O. V.	135.7	137.8	220	0
W. S.	332	349	870	4.9

were again placed on maintainance doses of Promizole, however, the urinary recoveries in all again ranged between 50 and 60 per cent of daily intake. The blood concentrations, however, showed the same tendencies as with the single equivalent doses. When 3 normal children were given 0.08 gm. per kg. of Promizole in a single dose, the urinary recoveries were 64, 82, and 83 per cent of the administered dose. The results of the above experiments are shown in table 4.

CONJUGATION OF PROMIZOLE IN URINE

Determinations of free and total Promizole were performed on twenty-four-hour urine specimens obtained from 7 tuberculous patients. The results are shown in table 5. It may be seen that only relatively small amounts of Promizole

are excreted in the urine in a conjugated form of the acetylation type. It is evident from these figures, however, that the urinary concentrations of the drug are far in excess of the known solubility of Promizole in aqueous solution, indicating that some conjugate has been formed, this involving some structure other than the diazotizable amine. Bambas and Vandenbelt have found by studies of physical characteristics and absorption spectra that this conjugate contains a Promizole nucleus with a substituted thiazole ring, the substitutions at both the nitrogen in the ring and that of the amine (21).

DISCUSSION

For the proper evaluation of Promizole in the treatment of tuberculosis, it is necessary to attain in each patient under therapy serum concentrations of the drug comparable with those which in animal experiments have been found therapeutically effective. As clinical studies progress, the analysis of clinical results may lend further evidence as to therapeutically effective drug concentrations. In the early studies with Promizole, it soon became apparent that the dose of Promizole necessary to obtain these blood concentrations varied greatly with different patients, some achieving them on a minute dose, others requiring immense doses of the drug.

From the pharmacologic studies performed, it would seem that absorption of the drug from the gastrointestinal tract is not a factor in the phenomenon. When the factors of the drug excretion, storage, and degradation are considered, various explanations are suggested, although none seems complete and satisfactory. In single-dose experiments, the combination of low recovery plus low blood concentrations suggests that storage of the drug in the tissues might explain the phenomenon. When these same patients are maintained on the drug for long periods until a time one might reasonably expect tissue saturation to have occurred, there is still no tendency for the blood concentrations to rise, despite continuation of the same dose. Individual differences in the capacity for destroying the drug do not appear to be the single determining factor in explaining discrepancies between dose and blood concentrations. Almost all patients studied have exhibited, when on maintenance regimens, the establishment of an equilibrium on which an average of 50 to 60 per cent of the daily intake is excreted. Even with this equilibrium, these patients have persisted in demonstrating the individual tendencies toward either high or low blood concentrations. It is hoped that long-term balance studies, now planned, may offer additional information.

The possibility was considered that other diazo compounds in the blood may have been interfering with the determination of Promizole, thus leading to apparent high levels. To discount this possibility, the children who exhibited high blood concentrations were taken off the drug, and studies in Promizole dissipation were performed. In all cases the blood was completely cleared in thirty-six to forty-eight hours, all subsequent determinations proving negative. In addition, the chemical methods for determining Promizole were performed on sera and urines of normal and tuberculous children who had never received the drug.

No false reactions were encountered. It must be remembered that other sulfones will give the same reaction and that the determination will represent the combined value of the sulfone and Promizole. Further studies are now in progress on plasma binding of Promizole, kidney and liver function, and, in addition, a search is being made for various degradation products which may not be measured by present methods. Preliminary work by Bambas (22) has indicated that such a product may actually exist, and further studies on this problem are being performed.

From the practical viewpoint, however, it seems fairly evident that the daily dose of Promizole and the interval of drug administration must be determined by the individual characteristics of the patients. It is our policy at present to begin with 0.5 to 1 gm. daily, guided by age, divided into 4 doses given every six hours. Blood concentrations are determined, and the dose gradually adjusted to give a blood concentration of 1 to 2 mg. per 100 cc.

Factors influencing the emergence of resistant variants of *M. tuberculosis* are constantly being studied. The addition of Promizole to streptomycin in the treatment of tuberculosis is one such factor. Careful analysis of the Promizole blood concentrations with full appreciation of the individual variability in obtaining effective therapeutic leads is essential. Only when adequate Promizole blood concentrations exist is an appraisal of the value of Promizole in preventing the emergence of resistant strains justified.

The one generalization which seems permissible is that those children who attain high peak concentrations on small doses (1 gm. daily) may be given the drug at twelve-hour intervals, but those requiring large doses to achieve therapeutic concentrations must be given the drug every six hours.

It should be mentioned here that no significant toxicity has been encountered in the use of Promizole except the goitrogenic effect. This latter reaction is seen usually after the patient has been on the drug for several months. Occasionally in the early period of therapy, abdominal distention, cyanosis, and vomiting may be observed. A red urine, microscopically and chemically negative for blood, may occur intermittently and is not significant.

SUMMARY

The dose of Promizole necessary to maintain adequate concentrations of the drug in the blood varies markedly from patient to patient. This phenomenon is not due to differences in absorption and is not satisfactorily explained by differences in urinary excretion, tissue storage, or capacity for drug destruction.

The dose of Promizole must be ascertained for each individual patient, guided by determinations of blood concentrations. An appreciable number of patients will receive inadequate amounts of the drug if calculation of the dose is made by age or weight.

Studies of absorption, excretion, distribution, and conjugations of Promizole have been presented.

SUMARIO

El Promizol en el Tratamiento de la Tuberculosis. Factores que Determinan la Dosificacion Adecuada

La dosis de Promizol necesaria para mantener concentraciones adecuadas de la droga en la sangre manifiesta una notable variabilidad de enfermo en enfermo. Este fenómeno no se debe a diferente absorción ni lo explican satisfactoriamente diferencias en la excreción urinaria, fijación en los tejidos o capacidad para destrucción de la droga.

Por medio de la determinación de las concentraciones sanguíneas, hay que averiguar la dosis de Promizol para cada enfermo dado. Si se calcula la dosis por edad o peso, un número apreciable de pacientes recibirá cantidades inadecuadas de la droga.

Se presentan aquí estudios relativos a la absorción, excreción, distribución y conjugaciones del Promizol.

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AN EVALUATION OF METHODS OF TESTING THE VIRULENCE OF ACID-FAST BACILLI[1]

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INTRODUCTION

Although acid-fast bacilli can be demonstrated readily by microscopic and cultural procedures, the only sure method of determining the virulence of these microorganisms has been by use of appropriate animal inoculation. From time to time workers have suggested new techniques for rapid determination of virulence of acid-fast bacilli. Among the most interesting of the newer tests have been the intradermal skin tests of Lester (1), the description of microscopic morphology of colonies in certain specific media (2), and reactions of the bacilli with specific chemical agents (the cytochemical reaction) (3).

It was the purpose of the investigation herein reported to study the correlation between these tests of virulence and the classical determination of virulence by animal inoculation.

Materials and Methods

Harvest of bacilli: Stock strains and freshly isolated strains of tubercle bacilli were selected and grown in Dubos Tween-albumin medium (4) (0.02 per cent Tween) for two weeks at 37°C. Each strain was tested by the cytochemical reaction ten times and twice by each of the other methods for testing virulence. Examinations for contamination of the cultures were made by microscopic study just prior to cytochemical testing. An aliquot of the young cultures in liquid medium was removed for weighing. Determinations of dry weight of the bacilli per unit volume of medium were made by washing the cells free of medium with sterile distilled water and drying in an oven at 180°C. for one hour.

Cytochemical testing: On the day the cytochemical testing was to be performed, two flasks of culture were prepared for each strain, with a known weight of bacilli per given volume of medium. Each culture was treated separately in the following manner. The culture was mixed thoroughly and 5 ml. were placed in each of six test tubes. Stained slides were prepared for an added search for contamination and for observation of serpentine growth. Five of the samples were centrifuged and washed twice in 50 per cent methanol for one hour at 37°C. The sixth tube was reserved for animal inoculation which was performed on the same day. The washed bacilli were resuspended in 5 ml. of buffer solution (5 per cent sodium chloride and 1 per cent sodium barbital, pH 9.46). The bacilli per tube varied in weight from 10 mg. to 1.5 mg., depending upon the strain. One milliliter of freshly prepared neutral red (10 mg. per 100 cc.) in aqueous solution was added to each of the first five tubes which were then well shaken to thoroughly mix the dye, buffer, and bacilli, thereby offering as much surface exposure of the cells to the dye as possible. The bacilli soon settled to the bottom, affording a good view of the color changes which appeared in five minutes and were complete in thirty minutes. It was noted that

[1] From Laboratory Services, Communicable Disease Center, Public Health Service, Federal Security Agency, Atlanta, Georgia.

the bacilli might be left overnight (twelve hours) in the buffer with no visible difference in the reaction on subsequently adding the dye. When the dye and buffer are mixed, a precipitate forms which remains in fine suspension. This occurs during the cytochemical test but will not interfere with the reading unless the latter is delayed an hour, or the tubes are centrifuged.

Observation of serpentine growth: One smear was made directly from each culture by withdrawing a few drops in a pipette. These were transferred to a slide and allowed to dry at room temperature. At first a general tendency toward parallel and end-to-end orientation of the cells was considered to be an indication of serpentine growth in the culture. Several smears appeared, however, which displayed a marked "river-of-logs" effect in "ropes" of bacilli over the slide, and which proved to be from cultures of *M. phlei* and the acid-fast "saprophyte-from-radish."[2]

Intradermal tests: For this test, injections were made intracutaneously into the shaved ventral surface of a guinea pig. The sites of injection were the four quadrants, i. e., the right and left sides, respectively, of the thorax and the lower abdomen. In this manner four separate strains may be tested on the same guinea pig, since one reaction does not affect the other. The inocula consisted of 0.01 mg. of bacilli in 0.1 ml. of sterile physiologic saline solution. The animals were examined at seven, ten, and fourteen days for evidence of induration, nodule formation, and ulceration at the site of injection. All guinea pigs used in this test were sacrificed and studied by gross and microscopic examination six weeks from the date of inoculation. Each strain was tested twice, using separate animals. Inoculations were made on the same day the other tests were performed.

Classical animal inoculation: The bovine strains of tubercle bacilli were injected intravenously into rabbits and the avian strain, intravenously into chickens. All others were injected subcutaneously into the right groin of guinea pigs. The rabbits and chickens were sacrificed three months after inoculation and the guinea pigs at the end of six weeks. The animals were examined at autopsy by gross and microscopic studies of lesions seen in the lymph nodes, spleen, liver, and lungs.

RESULTS

The results of the studies described above are summarized in table 1. Serpentine cords were seen, not only in two strains of saprophytes, *M. phlei* and the acid-fast "saprophyte-from-radish," but parallel orientation of the bacilli was noted in all of the virulent strains of tubercle bacilli as well.

The cytochemical test resulted in a strong positive reaction in the nine "wild" virulent strains tested, as well as in the acid-fast saprophyte from the radish. These reactions were bright red. Less intense colors were given by H37Rv and by one bovine strain (Copenhagen). A faint pink color was seen with bovine (Ravenel), avian (Kirchberg), BCG (Birkhaug), and H37Ra strains. The three other strains tested, *M. phlei*, *M. smegmatis*, and *M. butyricum*, exhibited no color change, the bacilli retaining their original creamy colors.

Inoculation of H37Rv and the nine "wild" strains into the groin of guinea pigs resulted in progression of the infection to the liver in all animals, and to the lung in most. Following inoculation with BCG (Birkhaug), the bacilli did not progress beyond the superficial and deep inguinal nodes. No involvement was found after

[2] This organism was obtained from the washings of a radish which was digested and cultured in the usual manner.

inoculation of *M. phlei*, *M. smegmatis*, and *M. butyricum*. The bovine strains inoculated into rabbits produced lesions of the lung, kidney, and spleen. Intravenous inoculation of the avian strain in the chicken caused small lesions in the lungs and kidneys.

Intradermal inoculations into guinea pigs of H37Rv, bovine (Copenhagen), bovine (Ravenel), and the nine freshly isolated human strains resulted in swelling at the site of inoculation in approximately seven days. Ulceration developed in two weeks, and at this time acid-fast bacilli could be demonstrated in the regional node by microscopic examination of smear preparations. The avian (Kirchberg) strain caused no ulceration or regional node involvement. BGC

TABLE 1

Comparison of Three Tests for Virulence of Acid-fast Bacilli with Standard Animal Inoculation Test

STRAIN OF ACID-FAST BACILLI	PARALLEL ORIENTATION (MICROSCOPIC EXAMINATION OF SMEAR)	CYTOCHEMICAL TEST*	ANIMAL INOCULATION†	LESTER TEST†
M. tuberculosis				
H37Rv	+	+Pink	+	+
H37Ra	+	±Very light pink	−	−
Bovine (Copenhagen)	+	±Light pink	+	+
Bovine (Ravenel)	+	±Very light pink	+	+
Avian (Kirchberg)	+	±Very light pink	+	−
9 wild strains‡	+	+Red	+§	+§
BCG (Birkhaug)	±	±Very light pink	+	−
M. phlei	+	−White	−	−
M. smegmatis	−	−White	−	−
M. butyricum	−	−White	−	−
Acid-fast "saprophyte from radish"	+	Red	−	−

* Each symbol represents ten cytochemical tests which were uniform for the given strain.

† Each symbol represents two tests.

‡ Nine strains were isolated from routine diagnostic specimens.

§ The guinea pig inguinal node only was positive. The Lester test showed no ulcer but the regional node contained acid-fast bacilli.

(Birkhaug) caused no ulcer, but acid-fast bacilli were found in the regional node. *M. phlei*, *M. smegmatis*, *M. butyricum*, the acid-fast saprophyte from the radish, and H37Ra caused no ulceration or regional node involvement when inoculated intracutaneously.

DISCUSSION

The intensity of the cytochemical reaction of acid-fast bacilli was uniform on repetition with a given strain but varied among different strains. Since all strains were tested in the same way[3], it may be assumed that variations in some intrinsic

[3] The slight variation in numbers of bacilli per tube is considered of no significance as an excess of dye was used and ample time was allowed for completion of the reaction.

biological characteristic from strain to strain causes a varying reaction when studied by the method described.

Fourteen strains of virulent tubercle bacilli were subjected to the cytochemical test. Nine of these strains were isolated from patients during routine diagnostic procedures. Four were laboratory strains; two, bovine; one, avian; and one, the human strain H37Rv. All of these strains showed virtually the same degree of virulence on animal inoculation, while cytochemical testing among these virulent strains showed varying degrees of intensity.

All of the strains recently isolated from infected humans showed more intense cytochemical reactions than did the stock strains which had been carried for some time in the laboratory, even though the latter had been passed through animals at three-month intervals. This might have been expected since most laboratory strains of tubercle bacilli tend to lose virulence after many transfers on artificial media. Disregarding the intensity of the reaction, all strains which subsequently proved, by classical animal inoculation, to be virulent proved also to be positive on cytochemical testing by showing some degree of color change. The positive cytochemical test, however, was not specific for virulent strains alone. A markedly positive reaction, as intense as those seen among the "wild" strains, was also seen in the acid-fast saprophyte isolated from a radish which proved on animal inoculation to be avirulent.

The attenuated strain, BCG (Birkhaug), showed a positive cytochemical test of slight intensity while the classical guinea pig inoculation test with this organism showed only a localized lesion in the inguinal node. The intracutaneous Lester test showed no ulcer, but a positive smear was obtained from the regional node, as might have been expected.

The human avirulent variant, H37Ra, showed a slightly positive cytochemical reaction, while classical animal inoculation, as well as the Lester test, proved it to be avirulent.

The saprophytes showed no reaction on cytochemical testing except for the acid-fast saprophyte from the radish, which gave an intense reaction. These saprophytes all proved to be nonpathogenic on animal inoculation.

Little correlation was noted between serpentine growth in the Tween-albumin medium (4) (0.02 per cent Tween) and virulence as determined by animal inoculation. There was a closer correlation when observations were made of parallel orientation of the bacilli. Dubos (2) has pointed out that cord formation is diminished in liquid medium when concentrations of more than 0.01 per cent Tween are used. This factor appears to have been operative in the tests reported above. Only two of the acid-fast bacilli showed true serpentine growth, and these were saprophytes. A tendency to parallel orientation was noted, however, in all of the virulent strains of tubercle bacilli. The acid-fast saprophyte from radish gave a positive cytochemical test while another saprophyte (*M. phlei*) gave a negative cytochemical test. Both were negative on animal inoculation.

The above observations indicate that one cannot rely solely on the findings by cytochemical testing and colony appearance to determine virulence of acid-fast bacilli. While all of the known virulent strains appear to yield a positive test,

some of the nonpathogenic saprophytes appear also to give the same positive findings.

The Lester test proved to be positive in all strains which were found to be pathogenic on animal inoculation except the avian strain (Kirchberg). This laboratory strain, however, is not as pathogenic as freshly isolated avian strains. BCG (Birkhaug) produced no ulcer on Lester testing but was found in the regional node. Both ulceration and demonstration of acid-fast bacilli in the regional node are necessary for the Lester test to be called positive.

SUMMARY AND CONCLUSIONS

Nineteen strains of acid-fast bacilli, thirteen virulent, one attenuated, and five saprophytic, were examined with four tests for virulence. Each strain was tested twice. Five cytochemical tests per culture were performed with each culture. All tests were controlled by appropriate animal inoculations.

The cytochemical reaction on repeated testing was constant for any given strain, but varied among different strains. The intensity of the cytochemical reaction was not directly related to the degree of virulence of various acid-fast bacilli in animals. All strains which proved to be virulent on animal inoculation were also positive by cytochemical test. Some strains which were positive by cytochemical test, however, were proved nonvirulent by animal inoculation.

There is little correlation between serpentine cords in cultures grown in Tween-albumin medium (Tween 0.02 per cent), as noted microscopically, and virulence as determined by animal inoculation. Parallel orientation of the bacilli noted microscopically correlated fairly well with virulence as determined by animal inoculation. A good correlation could also be demonstrated between parallel orientation and a positive cytochemical test. A good correlation was demonstrated between the Lester intradermal skin test and classical animal testing.

It appears, therefore, that the most reliable test for virulence remains appropriate animal inoculation with careful study of the animals at autopsy.

SUMARIO Y CONCLUSIONES

Justipreciación de las Técnicas Empleadas para Comprobar la Virulencia de los Bacilos Acidorresistentes

Diecinueve cepas de bacilos ácidorresistentes (trece virulentas, una atenuada y cinco saprofitas) fueron estudiadas con cuatro pruebas de virulencia. Cada cepa fué comprobada dos veces. Con cada cultivo se ejecutaron cinco ensayos citoquímicos. Todas las pruebas fueron cotejadas con apropiadas inoculaciones en animales.

Al repetirlo, el ensayo citoquímico se mostró constante para cada cepa dada, pero varió entre las diversas cepas. La intensidad de la reacción citoquímica no corresponde al grado de virulencia revelada por los varios bacilos ácidorresistentes al ser comprobados en animales. Todas las cepas que resultaron virulentas a la inoculación en animales también fueron positivas en el ensayo citoquímico, pero algunas de las positivas con el ensayo citoquímico mostráronse avirulentas en la inoculación en animales.

Existe, según se observó microscópicamente, poca correlación entre los cordones serpentinos en los cultivos sembrados en el medio de Tween-albúmina (Tween 0.02%) y la virulencia determinada por la inoculación en animales. La orientación paralela de los bacilos, observada microscópicamente, correlacionó bastante bien con la virulencia determinada por la precitada inoculación. Pudo también descubrirse buena correlación entre la orientación paralela y la positividad del ensayo citoquímico. Notóse ademas buena correlación entre la intradermorreacción de Lester y la clásica comprobación en animales.

Parece, pues, que la prueba más fehaciente de la virulencia continúa siendo la apropiada inoculación en animales con el cuidadoso estudio de los animales en la autopsia.

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STUDIES ON METHODS FOR DETERMINING SENSITIVITIES OF TUBERCLE BACILLI TO TIBIONE[1, 2]

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INTRODUCTION

Since the reports of the German experience with thiosemicarbazone compounds (1, 2, 4, 6) considerable interest has been aroused in this country in the use of this drug for the treatment of tuberculosis. Other than a tentative and preliminary recommendation by the Laboratory Committee for use by Veterans Administration Study Units (8), no method for determining sensitivity of tubercle bacilli to the drug has been described. The following work was undertaken to establish routine methods for testing sensitivity of tubercle bacilli to Tibione.

Methods

The solid medium employed was the American Trudeau Society egg-yolk medium (8) and the liquid medium was the Dubos-Davis Tween-albumin medium (3). The solid medium was tubed in screw-top vials and the liquid medium in 22 by 175 mm. tubes in 5 ml. amounts and in 19 by 150 mm. Coleman tubes in 10 ml. volumes. The latter were employed for spectrophotometer readings at 520 mu in the Coleman Junior spectrophotometer. All inocula from previously prepared cultures in Tween-albumin medium were standardized as described in an earlier paper from this laboratory (5). Concentrates of specimens of sputum were prepared by standard digestion procedures using 4 per cent sodium hydroxide.

Although Tibione is only slightly soluble in water, it is soluble in propylene glycol to the extent of 1 per cent at room temperature (7). The latter solvent was therefore chosen for preparing dilutions of the drug. A 0.5 per cent solution of Tibione in propylene glycol may readily be made. Heating hastens solution and does not result in deterioration of Tibione (7). Dilutions of this solution are made with Tween-albumin medium or with distilled water. A suitable range of concentrations of Tibione has been found to be from 50 to 0.01 γ per ml. These may be prepared conveniently by the double 1:10 serial dilution method as shown in table 1. Slight cloudiness sometimes develops in solution B, but heating quickly redissolves the precipitate.

RESULTS

The use of propylene glycol as a solvent made it necessary to test its effect on the growth of tubercle bacilli and on their sensitivity to other agents. The results of tests performed in liquid medium are shown in tables 2 and 3. Growth was measured in a Coleman Junior spectrophotometer at 520 mu. The inoculum used

[1] From the Streptomycin Research Laboratory, Laboratory Services of Veterans Administration Hospital, Staten Island, N. Y.

[2] Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

TABLE 1

Preparation of Dilutions of Tibione

SOLUTION	DILUTION	CONCENTRATION OF PROPYLENE GLYCOL	CONCENTRATION OF TIBIONE
		per cent	*γ per ml.*
A		100	5,000
B	1:50 of solution A	2	100
C	1:100 of solution A	1.0	50
D	1:10 of solution B	0.2	10
E	1:10 of solution C	0.1	5
F	1:10 of solution D	0.02	1
G	1:10 of solution E	0.01	0.5
H	1:10 of solution F	0.002	0.1
I	1:10 of solution G	0.001	0.05
J	1:10 of solution H	0.0002	0.01

TABLE 2

Effect of Propylene Glycol on Growth and Streptomycin Sensitivity of a Sensitive Strain of M. Tuberculosis

CONCENTRATION OF STREPTOMYCIN	GROWTH AFTER INCUBATION FOR TWELVE DAYS (Readings of Per Cent Transmission at 520 mu)					
	Per cent propylene glycol					
	0	1 per cent	2 per cent	3 per cent	4 per cent	5 per cent
γ per ml.						
0.0	45.0	46.0	50.0	54.0	57.0	69.0
0.1	45.5	51.0	54.0	61.0	63.5	78.0
0.2	45.5	58.0	61.5	66.0	77.0	89.5
0.3	49.0	59.0	60.0	84.5	87.0	92.0
0.4	52.0	64.5	83.0	92.0	93.0	92.0
0.5	54.0	75.0	92.5	93.0	93.0	93.5

TABLE 3

Effect of Propylene Glycol on Growth and Streptomycin Sensitivity of a Resistant Strain of M. Tuberculosis

CONCENTRATION OF STREPTOMYCIN	GROWTH AFTER INCUBATION FOR FOURTEEN DAYS (Readings of Per Cent Transmission at 520 mu)					
	Per cent propylene glycol					
	0	1 per cent	2 per cent	3 per cent	4 per cent	5 per cent
γ per ml.						
0	39.0	42.0	46.5	53.0	61.0	75.0
1	38.5	42.0	46.5	49.5	62.0	78.0
10	38.0	42.0	47.5	54.0	63.0	77.0
100	39.5	44.5	47.5	54.5	60.5	78.0
500	41.5	50.0	55.5	56.0	75.5	69.5
1,000	43.5	43.0	49.0	54.5	63.0	72.0

was 0.2 ml. of a 7-day-old culture adjusted to 70 per cent transmission at 520 mu. This inoculum corresponded to 2×10^{-5} gm. dry weight of tubercle bacilli. In table 2 are shown data on the effects of 1 to 5 per cent propylene glycol on growth and sensitivity of a streptomycin-sensitive strain. The data in table 3 show the effect of propylene glycol on a streptomycin-resistant strain. As may be seen, growth of both the sensitive and resistant strains was markedly affected by concentrations of propylene glycol greater than 1 per cent. Sensitivity to streptomycin of the sensitive strain was slightly but progressively increased as propylene glycol concentration was increased, whereas the resistant strain showed no effect

TABLE 4

Effect of Propylene Glycol on Growth of M. Tuberculosis H37Rv on Solid Medium

Thirty-five days' incubation

	PER CENT PROPYLENE GLYCOL					
	0	1	2	3	4	5
Growth	4+	4+	4+	3+	2+	0

TABLE 5

Effect of Inoculum Size on Sensitivity of M. Tuberculosis H37Rv to Tibione in Tween-albumin Medium

CONCENTRATION OF TIBIONE	GROWTH AFTER INCUBATION FOR FOURTEEN DAYS (Readings of Per Cent Transmission at 520 mu)					
	Grams inoculum per 10 ml. of medium					
	2×10^{-3}	2×10^{-4}	2×10^{-5}	4×10^{-5}	6×10^{-5}	1×10^{-4}
γ per ml.						
0.0	47.5	41.0	36.5	37.0	34.0	33.0
0.01	59.0	48.5	44.5	42.0	38.0	39.0
0.05	89.0	89.5	80.0	73.0	68.0	58.0
0.1	89.0	90.5	87.0	83.0	77.0	71.0
0.5	89.0	90.0	88.0	85.0	84.0	78.0
1.0	89.5	88.0	87.0	86.0	84.5	79.0
5.0	90.0	90.0	88.0	87.0	82.5	77.5

on sensitivity in the ranges studied. Similar results were obtained in the tests performed on solid medium (table 4).

The effect of the size of inoculum on the inhibitory concentration of Tibione was studied both in liquid and on solid medium. Inocula were prepared from 7-day-old cultures in Tween-albumin medium, adjusted to 70 per cent transmission according to the method described elsewhere (5). The size of the inoculum varied from 10^{-4} gm. dry weight of bacilli to 2×10^{-7} gm. in the liquid medium, and from 5×10^{-5} gm. to 7×10^{-6} gm. dry weight on the solid medium. The results are recorded in tables 5 and 6.

From the data in table 5, it may be seen that in liquid medium, as the size of the inoculum increased, sensitivity to Tibione decreased. In liquid medium, a

500-fold increase in size of inoculum resulted in a tenfold decrease in sensitivity to Tibione. On solid medium, this effect was seen in a somewhat different form. As the size of inoculum increased, the sharp break in the amount of growth occurring between 1 and 5γ per ml. remained, but an increasing amount of growth

TABLE 6

Effect of Size of Inoculum on Sensitivity of M. Tuberculosis H37Rv to Tibione on Solid Medium

CONCENTRATION OF TIBIONE	GROWTH AFTER THIRTY-FIVE DAYS' INCUBATION			
	Size of inoculum in grams			
	0.7×10^{-6}	1.25×10^{-6}	2.5×10^{-6}	5×10^{-6}
γ *per ml.*				
0.0	4+	4+	4+	4+
0.01	4+	4+	4+	4+
0.05	4+	4+	4+	4+
0.1	4+	4+	4+	4+
0.5	4+	4+	4+	4+
1.0	4+	4+	4+	4+
5.0	30 colonies	1+	2+	3+
10.0	30 colonies	1+	1+	1+
50.0	–	100 colonies	30 colonies	1+

TABLE 7

*Comparison of Liquid and Solid Media in Testing a Tibione-resistant Strain of M. Tuberculosis**

TIBIONE CONCENTRATION	LIQUID MEDIUM	SOLID MEDIUM
γ *per ml.*		
0.0	4+	4+
0.01	4+	4+
0.05	4+	4+
0.1	4+	4+
0.5	4+	4+
1.0	4+	4+
5.0	4+	4+
10.0	–	4+
50.0	–	4+

* The inoculum was prepared from a subculture made seven days previously from the 50γ per ml. tube in the last column of table 6. The growth was adjusted to 70 per cent transmission at 520 mu and the inoculum consisted of 2.5×10^{-6} gm. dry weight of bacteria for the solid medium and 10^{-6} gm. for the liquid medium. The liquid medium titrations were carried only as far as 5γ per ml.

occurred in the presence of higher concentrations of Tibione (table 6). Subculture from solid-medium tubes containing concentrations of Tibione of 10 and 50 γ per ml. resulted in growth in both liquid and solid media, indicating that this increased growth was resistant to Tibione (table 7).

The sensitivity to Tibione of a number of strains of tubercle bacilli was meas-

TABLE 8

Direct Inoculation of Concentrated Specimens of Sputum on Solid Medium

TIBIONE CONCENTRATION	GROWTH AFTER THIRTY-FIVE DAYS' INCUBATION				
	G6(9)*	G11(4)	G12(2)	G40(6)	I67(5)
γ per ml.					
0.0	4+	4+	4+	4+	4+
0.01	4+	4+	4+	4+	4+
0.05	4+	4+	4+	4+	4+
0.1	4+	4+	4+	4+	4+
0.5	1+	4+	3+	4+	4+
1.0	1+	4+	2+	4+	4+
5.0	0	0	0	3 colonies	0
10.0	0	0	0	40 colonies	0
50.0	0	0	0	0	0

* Figure in parentheses is the Gaffky number of the specimen.

TABLE 9

Tibione Sensitivity Tests in Liquid Medium of Various Strains of M. Tuberculosis

TIBIONE CONCENTRATION	GROWTH AFTER FOURTEEN DAYS' INCUBATION*								
	Streptomycin-resistant Strains					Streptomycin-sensitive Strains			
	RAR	PsR	SUR	RVR	SsR	RAS	U6S	U9S	RVS
γ per ml.									
0.0	4	4	4	4	4	4	4	4	4
0.01	4	4	4	4	4	2	4	4	4
0.05	1	3	4	4	3	0	2	3	1
0.1	0	1	1	1	1	0	1	1	0
0.5	0	0	0	0	0	0	0	0	0
1.0	0	0	0	0	0	0	0	0	0
5.0	0	0	0	0	0	0	0	0	0

* Readings given arbitrary comparison values. A 4+ reading is maximum growth.

TABLE 10

Tibione Sensitivity Test in Liquid Medium of Two Strains of M. Tuberculosis

TIBIONE CONCENTRATION	GROWTH AFTER FOURTEEN DAYS' INCUBATION (Reading of Per Cent Transmission at 520mμ)	
	RVR	RVS
γ per ml.		
0.0	46.0	46.5
0.01	47.8	48.0
0.05	47.2	64.3
0.1	80.0	84.0
0.5	89.0	89.0
1.0	90.8	89.0
5.0	91.3	90.0

ured by both techniques to check the efficacy of the methods. The inoculum employed for the tests with solid medium consisted of 0.5 ml. of a concentrated specimen of sputum. Liquid medium inocula consisted of 0.1 ml. of Tween-albumin medium suspension per 5 ml. of medium. The results with solid medium tests are shown in table 8, and those with liquid medium in tables 9 and 10.

Both methods resulted in satisfactory end points, but approximately a ten times greater concentration of Tibione was required to prevent growth on solid medium than in liquid medium. As may be seen from these data, most strains in liquid medium were inhibited by 0.5 γ of Tibione per ml., whereas on solid medium most strains were inhibited by 5 γ per ml.

A possible explanation for this discrepancy is found in the following experiment. Sensitivity to Tibione of several strains of tubercle bacilli was determined in liquid medium as previously described, except that Tween was omitted from

TABLE 11

Sensitivity of Strains of M. Tuberculosis to Tibione in Liquid Medium without Added Tween

TIBIONE CONCENTRATION	GROWTH AFTER FOURTEEN DAYS' INCUBATION			
	RVR	RVS	U13	U32
γ *per ml.*				
0.0	4	4	4	2
0.01	4	4	4	2
0.05	3	2	3	2
0.1	2	2	2	2
0.5	1	±	±	1
1.0	±	±	±	±
5.0	±	±	±	±

± indicates a small amount of growth.

the medium. The results are listed in table 11. In the absence of Tween, Tibione was markedly less inhibitory to tubercle bacilli and the results obtained were very similar to those obtained with solid medium.

SUMMARY

A laboratory investigation has been made of methods for determining sensitivity of strains of *M. tuberculosis* to Tibione, employing both solid and liquid media. Preparation of media containing Tibione in concentrations of .01 to 50 γ per ml. is described, utilizing propylene glycol as the solvent.

Certain factors which may influence the results of the test were investigated. It was found that the effect of the solvent, propylene glycol, in concentrations below 1 per cent was small enough to be disregarded. The effect of the size of inoculum was also studied. In liquid medium, an increase in size of inoculum from 2×10^{-7} gm. to 10^{-4} gm. per 10 ml. of medium resulted in a tenfold increase in the concentration of Tibione required for inhibition of growth. On solid medium, the use of a heavy inoculation resulted in the growth of many resistant colonies in the higher concentrations of Tibione. Strains resistant to 10 to 50 γ

per ml. of Tibione were isolated. It was also found that omission of Tween from the liquid medium resulted in values for the sensitivities comparable to those obtained with solid medium.

SUMARIO

Estudios de Técnicas Dedicadas a Determinar la Sensibilidad de los Bacilos Tuberculosos a la Tibiona

Dos técnicas, una basada en el empleo de un medio sólido y la otra en el empleo de un medio líquido de Tween 80-albúmina, fueron investigadas para uso en la determinación de la sensibilidad de ciertas razas del *M. tuberculosis* a la tibiona. Descríbese un método para la preparación de medios que contienen tibiona a concentraciones de 0.01 a 50 γ por ml., empleando como solvente glicol propilénico. Investigóse el efecto del glicol propilénico sobre la proliferación y la sensibilidad a la estreptomicina. A una concentración inferior a 1 por ciento, el efecto resultó menospreciable.

También se estudió en medios tanto líquidos cuanto sólidos el efecto del tamaño del inóculo. En medio líquido, el aumento del tamaño del inóculo, de 2×10^{-7} gm. a 10^{-4} gm. por 10 ml. de medio, logró decuplicar la resistencia. En medio sólido, una inoculación intensa dió por resultado la aparición de muchas colonias resistentes. Se aislaron cepas resistentes a 10 a 50 γ por ml. Las sensibilidades determinadas en medio sólido no resultaron tan elevadas como las determinadas en medio líquido que contenía Tween. Al omitir el Tween del medio líquido, las sensibilidades encontradas fueron comparables a las observadas en medio sólido.

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LATE RESULTS OF THORACOPLASTY ACCORDING TO TYPE OF PULMONARY TUBERCULOSIS[1]

The Present Status of 254 Patients Two to Ten Years after Thoracoplasty

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INTRODUCTION

This report is an analysis of the late results of thoracoplasty in 254 patients with pulmonary tuberculosis operated upon during the ten-year period from December 1937 through December 1947 and followed for two to ten years after completion of the operation. All of these patients were operated upon by, or under the supervision of, one of us (J. D. S.). The standard thoracoplasty as described by Alexander (1), including resection of transverse processes, was used throughout this period. The study was carried out mainly in an attempt to determine whether any type or group of cases would be more suitable for primary pulmonary resection than for thoracoplasty.

COMPOSITION OF CLINICAL SERIES

The cases were classified according to the clinico-pathologic groups suggested by Rubin and Klopstock (2) and were divided into the following seven major groups according to the predominant type of disease present before thoracoplasty: (*1*) fibrocaseous tuberculosis; (*2*) fibroid tuberculosis; (*3*) caseocavernous tuberculosis; (*4*) tuberculosis associated with "tension" (large thin-walled) cavities; (*5*) tuberculosis associated with marked destruction of lung and bronchiectasis ("destroyed lung"); (*6*) unexpandable lung; (*7*) tuberculous empyema.

All patients have been classified according to the 1950 edition of *Diagnostic Standards*. The term "inactive" as used in the text and tables signifies that repeated cultures of the bronchopulmonary secretions became and remained negative for tubercle bacilli, the appearance of lesions in serial roentgenograms was stable without roentgenologic evidence of cavity, and symptoms of tuberculous origin were absent (3).

In this series of 254 patients, 131 were males and 123 were females. There were 246 white patients, 4 Negroes, 3 Indians, and one Latin-American, and the ages ranged from 16 to 63 years (see table 1). An average of 4.6 thoracoplasty stages was performed per patient and an average of 7.5 ribs was resected per patient. All patients were classified as to their suitability for thoracoplasty both from the standpoint of operative risk and the probability of control of their disease. This classification was based on clinical, roentgenologic, and bronchoscopic examinations, as well as on family and personal history. Of the 254 cases, 64 were consid-

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ered good candidates for the operation, 58 average, and 132 below average. Active, bilateral disease was present in 187 (73.6 per cent) cases at the time of operation.

TABLE 1

Age Distribution in Patients Treated with Thoracoplasty for Pulmonary Tuberculosis

AGE	PATIENTS
years	
Less than 20	11
21 to 30	99
31 to 40	77
41 to 50	59
51 to 60	5
More than 60	3
Total	254

TABLE 2

Status of the Contralateral Lung at Time of Thoracoplasty

TYPE OF DISEASE	NUMBER OF PATIENTS	NO CONTRALATERAL DISEASE	INACTIVE CONTRALATERAL DISEASE	ACTIVE CONTRALATERAL DISEASE
Fibrocaseous	137	33	3	101
Fibroid	27	7	1	19
Caseocavernous	15	4	0	11
Tension cavity	45	7	0	38
Destroyed lung	23	6	2	15
Unexpandable lung	2	1	0	1
Tuberculous empyema	5	2	1	2
Total	254	60	7	187

RESULTS IN ALL PATIENTS

The 193 patients whose disease was classified as inactive following thoracoplasty had 847 negative cultures of sputum (average, 4.4 per patient) and 1,288 negative cultures of gastric aspirates (average, 6.7 per patient). It must be pointed out that patients operated upon in 1938 and 1939 had comparatively few cultures of gastric contents. Most patients in this series had gastric aspirations performed on three successive days every three months until cultures of the specimens became negative. After becoming inactive, the series of gastric aspirations were repeated three or more times prior to discharge from the sanatorium.

Following thoracoplasty, the patients remained at bed rest for at least six months. Exercise was gradually increased during the next six months and patients were discharged one year after the operation, provided that cultures of the gastric contents had been persistently negative for at least six months.

The distribution of cases according to the aforementioned classification is shown in table 2. Complications of pneumothorax caused all of the cases of empyema and unexpandable lung. In 2 of the patients with empyema and in both patients with unexpandable lung, negative cultures of pulmonary secretions were obtained prior to thoracoplasty.

In table 3 is shown the status of the contralateral lung before and after thoracoplasty. At some time before thoracoplasty, 38 patients had received contralateral

TABLE 3

Status of the Contralateral Lung Before and After Thoracoplasty

	BEFORE THORACOPLASTY	AFTER THORACOPLASTY		
		Progressive	Regressive	Stationary
Apparently clear	60	2	0	0
Apparently inactive	7	0	0	7
Active, stationary	113	11	10	92
Active, regressive	70	4	48	18
Active, progressive	4	1	3	0
Total	254	18	61	117

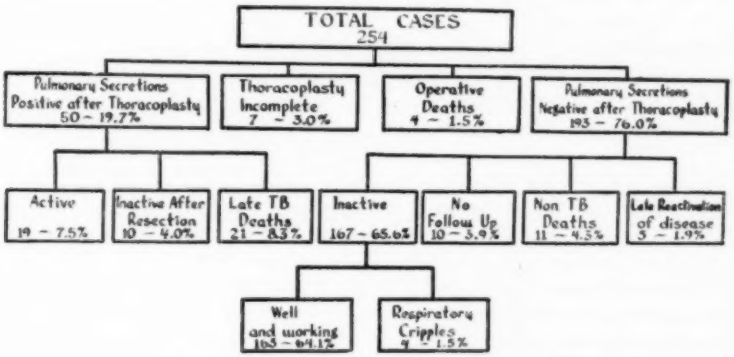

FIG. 1. Present status of all patients in series

intrapleural pneumothorax. Following thoracoplasty, intrapleural pneumothorax for the control of contralateral disease was used in 14 cases and extrapleural pneumonolysis followed by paraffin filling in 11 cases. If these same patients were being considered today, streptomycin therapy would probably be used in preference to pneumothorax or in conjunction with pneumothorax. During thoracoplasty there were 18 instances of spread or reactivation of disease; of these, 5 were bilateral, 3 were ipsilateral, and 10 were contralateral.

The present status of the entire series is summarized in figure 1. Cultures of the pulmonary secretions were negative in 193 patients (76 per cent) after tho-

racoplasty. (In 4 of these, cultures were negative prior to thoracoplasty.) In 50 patients (19.7 per cent) cultures of the pulmonary secretions remained positive. Among the latter, 19 patients (7.5 per cent) still have active disease; 10 patients (4.0 per cent) have inactive disease after pulmonary resection; and there were 21 late deaths due to tuberculosis (8.3 per cent). Thoracoplasty was not completed in 7 patients (3.0 per cent) because of spreads of disease after the first or second stage in 6 patients and because of the development of acute glomerulonephritis in one. "Operative death" included any patient who died within three months of the last stage of thoracoplasty. There were 4 operative deaths (1.5 per cent). One death followed bile peritonitis due to rupture of the gall bladder. One was attributed to a deep tuberculous wound infection and renal insufficiency secondary to amyloid nephrosis. Two patients died of bilateral spreads following the second stage.

Of the 193 patients whose tuberculosis was controlled by thoracoplasty, 163 (64.1 per cent of all cases) are known to be well and working. Four patients (1.5 per cent) are classified as respiratory cripples since their respiratory reserves are too limited to permit them to engage in gainful occupation. A late follow-up was accomplished in all but 10 patients (3.9 per cent) who left the sanatorium against medical advice. All were inactive at the time of their departure.

Among those patients whose tuberculosis was controlled by thoracoplasty and who were discharged from the sanatorium with inactive disease, 11 have died (4.3 per cent) from causes unrelated to tuberculosis or thoracoplasty. Following discharge from the sanatorium, 8 patients (3.1 per cent) had exacerbations of their tuberculosis. Three of the latter subsequently had repeated negative cultures of their bronchopulmonary secretions and were again classified as inactive. Thus, 5 patients (1.9 per cent) remain classified as "late reactivations," having been initially inactive for two or more years following thoracoplasty.

Revision thoracoplasties were performed on 2 patients. Neither of these revisions resulted in conversion to negative of cultures of bronchopulmonary secretions. If a technically satisfactory thoracoplasty is performed initially, it is believed that revision is seldom indicated.

Deep wound infections occurred in 14 patients (5.5 per cent). Nine of the deep wound infections were tuberculous. Seven of these had had hydro- or pyo-pneumothoraces following therapeutic pneumothorax on the thoracoplasty side. Contamination of the wound may have resulted when old needle-tract infections were incised. These tuberculous wound infections occurred among patients operated upon early in the series.

ANALYSIS OF RESULTS ACCORDING TO TYPE OF DISEASE

Group 1. Fibrocaseous tuberculosis (figure 2): This group consisted of those patients manifesting productive and exudative, or "mixed" lesions which had been present with little change for a number of months. Cavities of small or moderate size were usually present. There were 137 cases of this type of which 104 (76.0 per cent) were discharged as inactive following thoracoplasty. In 29 patients (21.2 per cent), the cultures of pulmonary secretions were not converted

to negative. Nine patients still have active pulmonary disease, and 7 (5.1 per cent) are inactive after pulmonary resection. There were 13 (9.5 per cent) late deaths due to tuberculosis. Thoracoplasty was not completed in one patient because of a spread of disease after the first stage. There were 3 operative deaths (2.2 per cent) in this group. Of the 104 patients (76.0 per cent) who were dis-

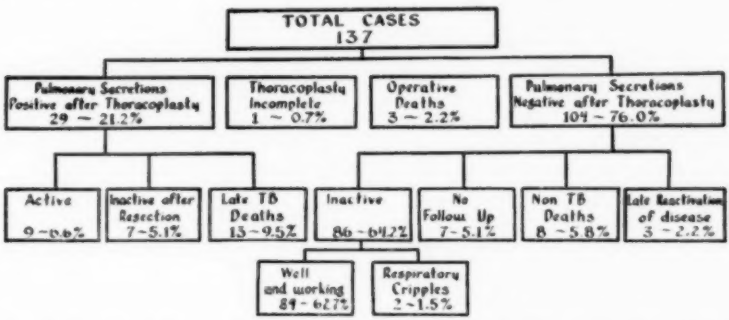

FIG. 2. Results of thoracoplasty for pulmonary tuberculosis in patients with predominately fibrocaseous disease.

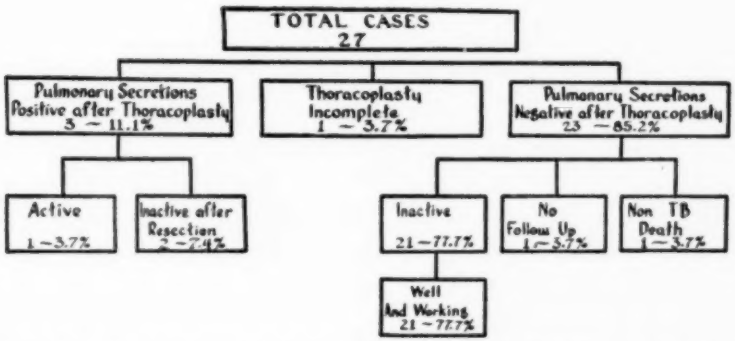

FIG. 3. Results of thoracoplasty for pulmonary tuberculosis in patients with predominately fibroid type of disease.

charged from the sanatorium with inactive disease, 84 (62.7 per cent) are well and working. Two are respiratory cripples. No late follow-up was obtained in 7 cases (5.1 per cent). Among the patients discharged with inactive disease, 8 (5.8 per cent) died of causes unrelated to tuberculosis. Three patients (2.2 per cent) had recurrence of disease two years or more after the completion of thoracoplasty.

Group 2. Fibroid tuberculosis (figure 3): This group was characterized by long-standing, dense, pulmonary fibrosis with retraction, cavities with rigid walls,

bronchiectasis, and compensatory emphysema. There were 27 patients in this group of whom 23 (85.2 per cent) were discharged as inactive following thoracoplasty. One patient (3.7 per cent) still has active pulmonary disease, and 2 (7.4 per cent) are inactive after pulmonary resection. Thoracoplasty was not completed in one patient (3.7 per cent) because of a spread of disease after the second stage. Twenty-one patients (77.7 per cent) are well and working. No late follow-up was obtained in one case (3.7 per cent). One death, unrelated to tuberculosis, occurred following discharge.

Group 3. Caseocavernous tuberculosis (figure 4): This group includes a relatively small number of patients having fairly extensive exudative tuberculosis with large cavities or cavities increasing in size. Of the total of 15 patients of this type, 11 (73.3 per cent) were discharged as inactive following thoracoplasty and are well and working. Two patients (3.3 per cent) still have active disease and

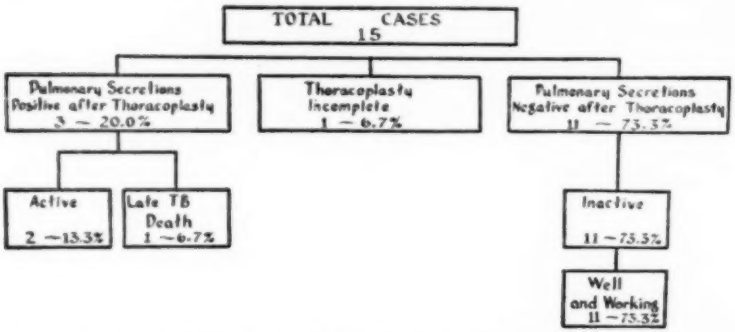

FIG. 4. Results of thoracoplasty for pulmonary tuberculosis in patients with predominately caseocavernous disease.

one (6.7 per cent) died of progressive tuberculosis. Thoracoplasty was not completed in one case (6.7 per cent) because of a spread after the second stage.

Group 4. Tuberculosis associated with "tension" (large thin-walled) cavities (figure 5): The principal lesion observed in this group was the so-called "tension cavity." In all of the patients, the cavities were located in an upper lobe. There were 45 patients in this group of whom 34 (75.5 per cent) were discharged as inactive following thoracoplasty.

Cavity drainages were performed on 16 of these patients. Open cavernostomies were performed after thoracoplasty on 7, and closed transpleural-type (Monaldi) drainages were performed prior to thoracoplasty on another 7. One patient had a Monaldi-type drainage before, and a cavernostomy after, thoracoplasty. One patient had a contralateral cavernostomy following thoracoplasty. The disease of 11 of the 16 patients on whom cavity drainage was performed became inactive.

Five patients (11.1 per cent) still have active disease and there were 2 late deaths (4.4 per cent) due to progressive tuberculosis. Thoracoplasty was not completed in 4 cases (8.9 per cent) because of spreads after the first or second

stage in 3 and the development of acute glomerulonephritis in one. Thirty-one patients (69.0 per cent) are well and working. No follow-up was obtained in one case. One patient is a respiratory cripple, and late reactivation of disease occurred in another.

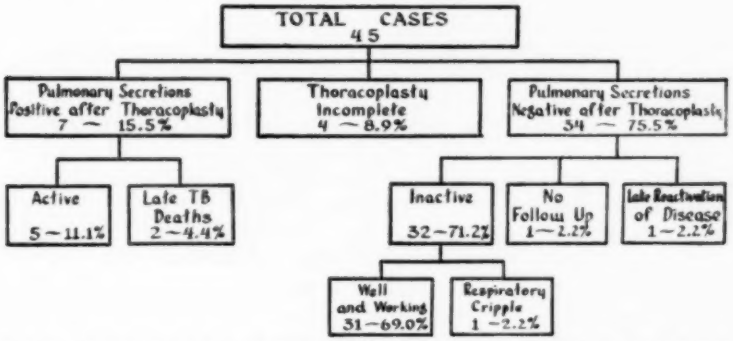

FIG. 5. Thoracoplasty for pulmonary tuberculosis associated with "tension" (large, thin-walled) cavities.

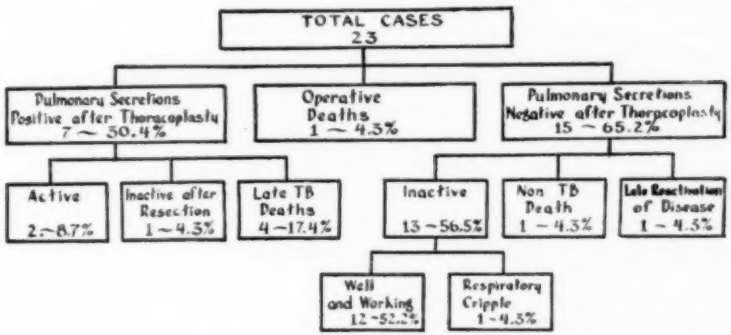

FIG. 6. Thoracoplasty for pulmonary tuberculosis associated with marked destruction of lung and bronchiectasis ("destroyed lung").

Group 5. Tuberculosis associated with marked destruction and bronchiectasis ("destroyed lung") (figure 6): This group consists of patients who had unilateral fibrotic and functionless ("destroyed") lungs. There were 23 patients of this type of whom 15 (65.2 per cent) were discharged as inactive following thoracoplasty.

Prior to operation, chronic tuberculous endobronchial disease was found in 15 patients (65.2 per cent), and in 11 the disease became inactive.

At some time before thoracoplasty, 8 of these patients had received pneumothorax treatment on the involved side. Two patients (8.7 per cent) still have

active pulmonary disease; one (4.3 per cent) has inactive disease after pulmonary resection; and there were 4 late deaths (17.4 per cent) due to tuberculosis. One operative death (4.3 per cent) was attributed to a deep tuberculous wound infection and amyloid nephrosis. Twelve patients (52.2 per cent) are well and working and one patient (4.3 per cent) is a respiratory cripple. One late death and one case of late recurrence of disease were unrelated to tuberculosis.

Group 6. Unexpandable lung: There were 2 patients with unexpandable lung in the series. Both of these represented complications of pneumothorax treatment, and both had negative cultures of bronchial secretions prior to thoracoplasty. One patient is well and working; the other died of heart failure two years after the operation.

Group 7. Tuberculous empyema: Thoracoplasty was performed on 5 patients for the treatment of tuberculous empyema, which in each instance was a complication of pneumothorax therapy. Two patients had negative cultures of bronchial secretions before operation. Extrapleural thoracoplasty was followed by Schede thoracoplasties in 4. Three patients in this group are now well and working; one was discharged with inactive disease but could not be followed; and one died of progressive pulmonary tuberculosis.

Tuberculous bronchitis: Tuberculous bronchitis has been considered separately in order to point out the results obtained by thoracoplasty performed during the acute stage of this complication as compared to results obtained when the operation was performed during the chronic stage of the disease.

Thirteen patients with acute ulcerative tuberculous bronchitis were operated upon. In 2 the disease became inactive. Long after thoracoplasty, an additional 5 became inactive after receiving streptomycin therapy.

Nineteen patients had chronic tuberculous bronchitis with fibrous bronchial stenoses. In 12 of these patients, the disease became inactive following thoracoplasty. One additional case became inactive following streptomycin therapy late in the post-thoracoplasty period.

Relatively few patients in this series received streptomycin. During the year of 1947, streptomycin prepared for thoracoplasty 9 patients gravely ill with extensive, exudative disease. The operation was started after six to eight weeks of streptomycin therapy, and the drug was continued throughout the thoracoplasties (4). These patients could not have been operated upon without streptomycin. Of these 9 patients, 8 are well and working and one still has active disease. In addition, streptomycin was administered late in the post-thoracoplasty period to 21 other patients in this series. The indications were: persistent tuberculous sinus, tuberculous bronchitis, and persistently positive pulmonary secretions long after thoracoplasty where resection did not appear feasible. Of these 21 patients, cultures of pulmonary secretions in 14 became and have remained negative.

DISCUSSION

This study was made in an attempt to determine, if possible, which types or groups of cases should be considered for primary pulmonary resection rather than for thoracoplasty. It is believed that the results of thoracoplasty in all

groups were satisfactory and that primary pulmonary resection should not be considered for any of the groups as a whole.

Poorest results were obtained in the patients classified as having a "destroyed lung." Most of these patients, however, were extremely poor surgical risks and it is doubted that primary pulmonary resection could have produced as good results in these patients as were obtained by thoracoplasty.

It is agreed that there are definite indications for primary pulmonary resection in pulmonary tuberculosis. No patient in this series presented these indications (lower lobe disease, "tuberculoma," et cetera).

Even though our patients were classified according to the same clinico-pathologic groups as the patients reported by Rubin and Klopstock, the results differ from theirs, particularly in certain groups. For example these investigators reported that they obtained the poorest results with thoracoplasty in patients having long-standing fibroid tuberculosis. The results in the present series were best in this group. There are inevitable discrepancies between reports of results of thoracoplasty (or any other procedure used for the treatment of pulmonary tuberculosis) from different centers because of individual variations in the interpretation of roentgenograms, variations in surgical techniques, and differences in racial and economic groups.

SUMMARY

This report presents the results of thoracoplasty for pulmonary tuberculosis in 254 patients followed for two to ten years. The patients were classified according to the clinico-pathologic type of disease present before thoracoplasty in an attempt to determine whether certain types of disease might be more suitable for primary pulmonary resection than for thoracoplasty.

The results in all groups were satisfactory and it is believed that primary pulmonary resection should not be considered for any of the groups as a whole.

SUMARIO

Resultados Tardíos de la Toracoplastia Conforme a la Forma de la Tuberculosis Pulmonar

Preséntanse los resultados de la toracoplastia por tuberculosis pulmonar en 254 enfermos mantenidos en observación durante dos a diez años. Tratando de determinar si ciertas formas de la enfermedad serían más adecuadas para la resección pulmonar primaria que para la toracoplastia, los casos fueron clasificados conforme a la forma clínicopatológica de enfermedad que había presente.

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TUBERCULOMA OF THE BRAIN[1,2]

Surgical Removal in the Presence of Widespread Tuberculosis

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INTRODUCTION

Tuberculomas of the brain are rarely encountered, and successful surgical removal is accomplished even more rarely. Opinions on the ultimate fate of patients with these lesions have varied from extreme pessimism to guarded optimism. Tuberculous meningitis has always been the most feared complication of surgery for tuberculoma. The presence of active tuberculosis elsewhere in the body may alter the prognosis and must be evaluated when craniotomy is considered. The introduction of streptomycin and other chemotherapeutic agents has improved the outlook for the patient. The successful removal of tuberculoma of the brain in the presence of widespread active tuberculosis elsewhere in the body seemed to us to be of sufficient interest to justify this report.

REVIEW OF THE LITERATURE

In 1890, Starr (1) noted that tuberculomas made up 50.8 per cent of all brain tumors in individuals below the age of 19 years. In 1893 he reported that 13.6 per cent of brain tumors in individuals over the age of 19 were tuberculomas (2). Subsequent reports have listed the incidence of tuberculoma over the wide range of 12.6 to 0.002 per cent of all brain tumors (3, 4, 5, 6, 7). These differences may be explained in part by the diminishing incidence of tuberculosis and by the fact that some series of cases are reported by neurosurgeons, while others are based on autopsy data. It is fairly well agreed today that tuberculomas constitute from 1 to 3 per cent of all brain tumors (4, 8, 9, 10, 11, 12).

Tuberculomas of the brain are always secondary to a focus elsewhere in the body, most commonly arising by hematogenous spread. They may occur at any age. Some series have noted their predominance in children (4, 8, 9, 11, 13) while other observers have found them more common in adults (10, 12, 14). All are agreed that they occur more frequently in males and Negroes. Although there are divergent reports (5, 10, 12, 16), tuberculomas are more likely to be single than multiple (7, 8, 9, 13, 14, 15).

There is considerable difference of opinion as to predominant location. Some have reported them most frequently in the cerebellum (1, 4, 8, 13, 14) while others have found them chiefly in the cerebrum (7, 9, 12). Lewison, Freilich, and Ragens (10) noted that they occur with equal frequency in these sites.

[1] From the Veterans Administration Hospital, Bronx, New York.

[2] Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Posterior fossa lesions are more likely to come to clinical attention and will therefore predominate in the groups of cases observed by the neurosurgeon. Next in frequency after the cerebrum and cerebellum are the pons and the basal ganglia. Tuberculomas of the meninges also occur.

Morphologically, cerebral tuberculomas are similar to productive lesions of tuberculosis elsewhere. They vary in size from 0.20 by 0.20 cm. to 4 by 8 cm. On microscopic examination, three layers are described. There is a central zone

TABLE 1

Reported Cases of Surgical Removal of Intracranial Tuberculoma

AUTHOR AND REFERENCE	NUMBER OF CASES	RESULT
Van Wagenen (4)	30 (cerebral)	25 died within one year
	12 (subtentorial)	11 died within one year
	15	All died
Garland and Armitage (5)	2	Both died of mengingitis
Cushing (8)	24	22 died within one year
		2 survivals (1 and 15 years)
Lewison, Freilich, and Ragens (10)	1 (cerebellar—case of Kwan)	11-year survival
Buchstein and Adson (17)	2 (meningeal)	1 died after 9 years (meningitis)
		1 alive after 9 months
	21 (cortical)	14 alive for periods up to 9 years
		1 died after operation
		6 died within 11 to 24 months
Dott and Levin (41)	94	51 deaths (11 postoperative deaths; 20 deaths due to meningitis; 12, tuberculosis elsewhere; 8, miscellaneous causes)
Vincent and Daum (42)	2 (cerebellar)	1 death (meningitis)
		1 alive after 5 years
	28 (cerebellar—cases of Aubin)	20 died in hospital
		3 died outside hospital
		4 alive (1½, 2, 4, and 9 years)
Alajouanine and Thurel (43)	1 (cerebral)	Died after 3 years (tuberculous meningitis)
Smith and Daniel (44)	6	4 survivals
		2 died of meningitis

of necrosis which is surrounded by a zone composed of giant cells, lymphocytes, plasma cells, polymorphonuclear leukocytes, and increased glial tissue. In this latter area tubercle bacilli may occasionally be demonstrated. This area is in turn surrounded by brain tissue showing degenerated nerve cells and nerve fibers. The small blood vessels are thrombosed and show lymphocytic cuffing. Fat-laden macrophages and hypertrophied astrocytes may be found in large numbers. Daughter tubercles often surround the main mass.

The clinical picture of tuberculoma of the brain is quite varied. The majority of patients are asymptomatic. Meningeal tuberculoma (tuberculoma en plaque)

may have its onset with Jacksonian seizures; the clinical course is often protracted, and death may occur from meningitis. Intra-encephalic tuberculomas, after becoming clinically manifest, usually progress rapidly, with death from meningitis or the effects of increased intracranial pressure. The exact symptomatology is dependent on the location of the lesion. Buchstein and Adson (17) have given an excellent discussion of the clinical course, and there are a number of case reports in the literature (4, 8, 11, 18–38). Approximately three-fourths of the cases terminate with tuberculous meningitis. In a small percentage, calcification and healing occur (39, 40).

The reported cases of surgically resected intracranial tuberculomas are outlined in table 1. In general, the surgical approach to tuberculoma has been viewed with pessimism. This is probably due largely to the influence of Cushing (8), whose poor results led him to advise decompression as the only surgical procedure. In contrast, Dott and Levin (41) believe that total removal of the lesion, when feasible, is the operation of choice. The poorest results have been reported in cases of cerebellar tuberculoma. Buchstein and Adson have pointed out that, because of the depth to which the interfolial septa of pial tissue penetrate the cerebellum, virtually every tuberculoma will be in contact with these septa at one or more points. Cerebellar tuberculomas are therefore difficult to remove completely and these authors recommend decompression for lesions in this location.

CASE REPORTS

Case 1. This 26-year-old Negro male was perfectly well until early in January 1948, when he first noted drenching night sweats. Two weeks later, he experienced a convulsive seizure during which he turned about uncontrollably, fell to the ground, and was unconscious for five minutes. He was not incontinent of urine or stool during the seizure. He was described as having turned his head to the right and moved his right arm. Upon awakening, he was dazed, complained of severe headache, and was completely amnesic for the incident. Night sweats and frequent chilly sensations persisted. On the supposition that he might be suffering from malaria, atabrine was administered by his physician but had no effect. Approximately a dozen similar seizures occurred up to March 9, 1948, when he was admitted to another hospital where he had several Jacksonian seizures involving the right side of the face, neck, and right arm. His temperature ranged between 99° and 103.2°F. Penicillin was administered without effect on the fever. On March 18, 1948 he was transferred to this hospital with a diagnosis of probable brain abscess. No additional facts of significance were elicited in his past history and review of systems.

Physical examination on admission: His temperature was 103°F.; pulse, 120 per minute; and respirations, 20 per minute. He appeared acutely and chronically ill. There was yellowish discoloration of the face and palms, thought to be due to previous intake of atabrine. The cervical, axillary, and inguinal lymph nodes were moderately enlarged and were soft, nontender, and freely movable. The lungs were clear to percussion and auscultation. A soft systolic murmur was audible over the cardiac apex. The tip of the spleen was palpable. The remainder of the general physical examination as well as complete examination of the nervous system showed no abnormalities.

Laboratory data: The concentration of hemoglobin in the blood was 8 gm. per 100 cc., and the erythrocyte count was 2.1 million per cu. mm. The leukocyte count was 5,200 per cu. mm., of which 66 per cent were polymorphonuclear leukocytes, 26 per cent lymphocytes, 7 per cent monocytes, and 1 per cent basophils. Urinalysis revealed one plus albumin and,

on microscopic examination, numerous leukocytes and erythrocytes. Blood test (Wasserman) was negative. Examination of the blood for sickling of erythrocytes was negative. Total plasma proteins were 7.6 gm. per 100 cc. (albumin, 2 gm.; globulin, 5.0 gm.). Icterus index was 5.2. Cephalin flocculation test was negative. Lumbar puncture yielded clear, colorless fluid under normal pressure. Cerebrospinal fluid protein was 26 mg. per 100 cc. There were no cells, and the colloidal gold curve was normal.

Several blood cultures were sterile. Numerous cultures of urine, including cultures for tubercle bacilli, were negative. Multiple examinations of specimens of sputum and gastric contents were negative on smear and culture for acid-fast bacilli. On June 9, 1948 the cerebrospinal fluid protein content was 101 mg. per 100 cc., and on August 18, 1948 colloidal

FIG. 1 Case 1. Arrow indicates destructive lesion of fourth lumbar vetrebra.

gold curve of the fluid showed moderate first-zone elevation. Aside from these findings, all studies of the cerebrospinal fluid, including cultures for pyogenic organisms, fungi, and acid-fast bacilli, revealed no abnormalities. The Frei test was negative.

An admission roentgenogram of the chest was normal, as were stereoscopic films of the skull. Intravenous pyelogram was within normal limits.

Course in the hospital: The admission studies did not yield a specific diagnosis. The patient's course was characterized by a spiking temperature up to 105°F. with a proportionately rapid pulse rate. Despite the fever, he felt remarkably well. The fever did not abate after administration of sulfadiazine and penicillin. Under observation, he had several right-sided convulsions which were always preceded by turning of the head and eyes to the right. During the seizures, which lasted no more than two minutes, the patient did not appear to be in complete contact but almost immediately after the fit, contact could be made. There was no post-convulsive paresis or aphasia.

On April 6, 1948, lymph nodes were removed from the right axillary and right cervical regions. Microscopic examination of sections of the nodes revealed the pathologic picture

of tuberculosis. Acid-fast bacilli were present in the sections. Streptomycin therapy was begun and 1 gm. was given daily for six weeks. No appreciable change was noted in the clinical course. On May 14, 1948 a retrograde pyelogram revealed irregularity in the region of the lower calyces of the right kidney. The chest roentgenogram at this time was within normal limits. He was then given Promin intravenously, 4 gm. daily for a total of three courses, each of two weeks' duration with a week of rest without treatment. At this time

FIG. 2 Case 1. (a) Exposed left parietal cortex. Markers point to area overlying the tuberculoma; (b) tuberculoma after removal.

he also received several blood transfusions. Following this, his temperature fell to levels ranging between 99° and 101°F.

In July 1948, approximately four months after admission, the roentgenogram of the chest revealed an area of translucency in the anterior segment of the third rib on the right. In August 1948 the patient complained of an aching in the left thigh, and it was noted that he walked with a limp. Roentgenograms revealed multiple areas of bone disease involving the ribs, lumbar vertebrae (figure 1), and left sacroiliac joint. The roentgenographic ap-

pearance of all of these lesions was compatible with tuberculosis. The orthopedic consultant advised conservative therapy. Another six-week course of streptomycin and three courses of Promin were given with no significant change in the clinical or roentgenologic findings.

In early October 1948, seizures became more frequent and, following each episode, the patient manifested paresis of the right arm and leg, right lower facial weakness, and mild motor aphasia. On several occasions, he developed a generalized convulsion following the initial focal movement. On October 19, 1948 he went into status epilepticus and developed a right hemiparesis and partial motor aphasia. By the following day he was having as many as thirty seizures a day. Intravenous barbiturates in large doses were required to stop the

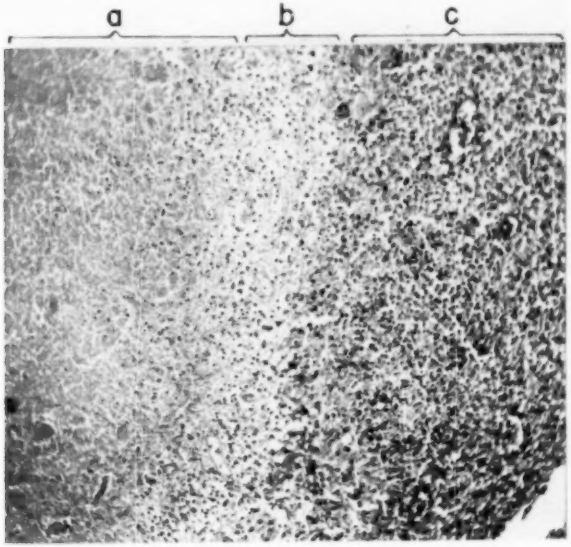

FIG. 3 Case 1. Photomicrograph of section of tuberculoma: (a) central zone of caseous necrosis; (b) area of cellular infiltration; (c) compressed brain tissue.

seizures. Pneumoencephalogram performed on November 4, 1948 was within normal limits. All the clinical evidence pointed to a well-localized lesion in the left cerebral cortex, most probably a tuberculoma.

On November 10, 1948 a left frontal Frazier type of craniotomy was performed. Exposure of the cortex revealed a whitish pale area measuring 1 cm. in diameter in the mesial frontal gyrus, approximately 1 cm. anterior to the motor cortex (figure 2a). On palpation, a hard lesion, approximately 2 cm. in diameter, was felt at a point 2 cm. below the cortex. A cortical block excision was made, and the mass together with a small area of adjacent white matter and adherent cortex were easily enucleated (figure 2b). Before leaving the operating room, the patient was able to move his right arm and leg well, and there was no evidence of facial weakness or speech disturbance. The diagnosis made by the pathologist (Dr. Abner Wolf) was tuberculoma (figure 3). Forty-eight hours postoperatively, the patient developed slight weakness of the right arm and a moderately severe motor aphasia. These symptoms

disappeared completely within three weeks, and examination of the nervous system at that time showed no motor or sensory defects.

All seizures ceased and his general condition was considerably improved. There was no significant change in other lesions of his generalized tuberculosis. In December 1948, Pott's abscess of the lower dorsal spine was first noted (figure 4a). Roentgenographic changes consistent with tuberculosis were also observed in both kidneys.

On April 17, 1949, five months after operation, he experienced a mild seizure. It was believed that this was probably due to scar formation. Following this, seizures recurred at intervals of one to two weeks. The patient was then placed on phenobarbital and dilantin therapy, and has had no seizures for the past three months (December 1949).

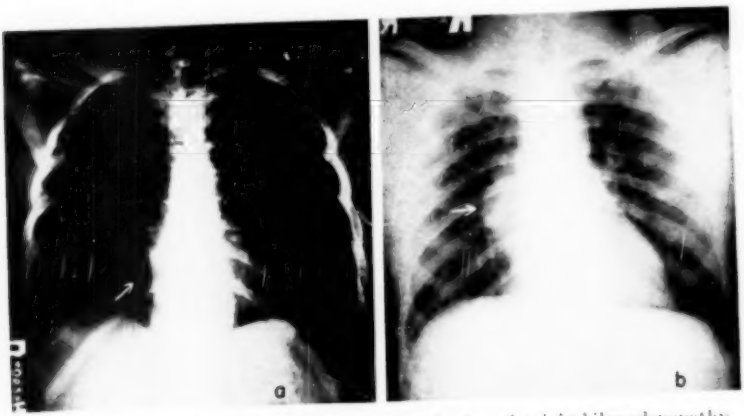

FIG. 4 Case 1. (a) Pott's abscess of lower dorsal spine; (b) right hilar adenopathy.

In May 1949, right hilar lymphadenopathy was first noted (figure 4b). In July 1949 a cold abscess of the subcutaneous tissue about the left shoulder appeared. Despite his extensive disease, the patient has continued to gain weight and has no complaints. The ultimate outlook remains very unfavorable. He is now under treatment with para-aminosalicylic acid.

Case 2. This 28-year-old Negro male was admitted to the hospital on April 19, 1949 complaining of severe headaches. One month prior to admission he had noted the gradual onset of throbbing bifrontal headaches which radiated to the occiput. The headache was worse in the morning on arising and was aggravated by coughing or straining. Left-sided tinnitus appeared at the same time and was followed by vertigo three weeks prior to admission. Diplopia and blurred vision, especially in the right eye, appeared two weeks before admission. Staggering gait had been present for ten days and it was noted that he veered to the left while walking. Diminished sensation and paresthesia over the left side of the face had also been noted. On admission, the headache was almost continuous and was associated with nausea and vomiting.

Past history revealed that cough, night sweats, and hemoptysis were noted in June 1947. A chest roentgenogram in November 1947 revealed pulmonary disease. Between December 1947 and August 1948 the patient had been hospitalized at intervals for chest disease; he had left against advice on several occasions. Data from the other hospitals indicated that the original pulmonary lesions had consisted of enlarged mediastinal lymph nodes and a small area of infiltration in the right upper lobe. Subsequently, a right pleural effusion

developed (figure 5a) and resorbed spontaneously. One examination of a concentrated specimen of sputum was reported as positive for acid-fast bacilli. Since August 1918 he had been under observation by the board of health, and his pulmonary disease had remained apparently stable.

Physical examination: The patient was markedly lethargic. Pulse and respirations were normal; blood pressure was 146 systolic and 110 diastolic in mm. of mercury. Percussion note over the right chest was impaired and the breath sounds were slightly diminished. The remainder of the routine physical examination was negative.

Examination of the nervous system revealed an ataxic gait with veering to the left, the patient being unable to walk without support. There was slight nuchal rigidity without a

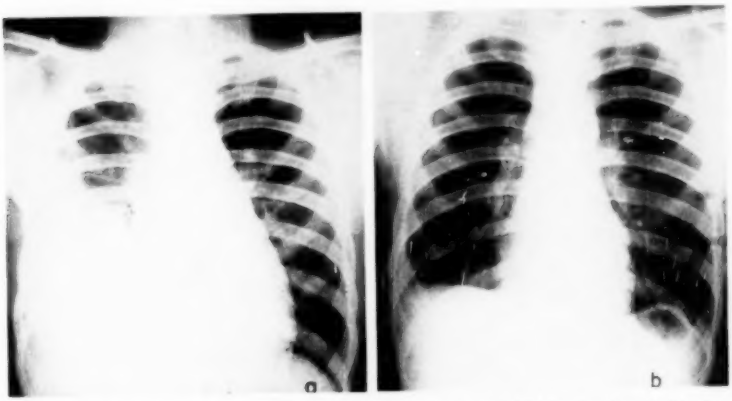

FIG. 5 Case 2. (a) Roentgenogram of the chest prior to admission showing right pleural effusion; (b) Roentgenogram of the chest on admission.

positive Kernig sign. Olfactory sensation was questionably impaired on the right. The left pupil was larger than the right, but both reacted well to light and attempts at near vision. There were three diopters of papilledema on the right and two diopters on the left associated with bilateral retinal hemorrhages. The left nasal reflex was diminished and the left corneal reflex absent. There was a mild right facial weakness of the peripheral type. Auditory acuity was greater on the right than on the left as tested by both air and bone conduction. All deep tendon reflexes were markedly depressed without associated weakness or wasting. Rapid alternating movements were performed slowly. Point-to-point tests were fairly well performed. Superficial reflexes were intact. There was a Gordon sign on the left. All sensory modalities were intact.

Laboratory data: The hemoglobin was 17 gm. per 100 cc.; the erythrocyte count, 5.3 million per cu. mm.; and the leukocyte count, 9,200 per cu. mm. Differential leukocyte count revealed 79 per cent polymorphonuclear leukocytes, 17 per cent lymphocytes, and 4 per cent monocytes. Urinalysis was normal. Fasting blood sugar was 104 mg. per 100 cc.; urea nitrogen, 15 mg. per 100 cc. Lumbar puncture yielded a slightly hazy fluid under increased pressure, with 90 erythrocytes and 2 lymphocytes per cu. mm. Chemical determinations on the cerebrospinal fluid showed the chlorides to be 700 mg. per 100 cc.; glucose, 86 mg. per 100 cc.; and protein, 196 mg. per 100 cc. The Wasserman test on the fluid was negative. The colloidal gold curve was flat. Smears and cultures of the cerebrospinal fluid yielded no pyogenic organisms or acid-fast bacilli.

On the day following admission, ventriculography disclosed dilatation of both lateral

ventricles, the third ventricle, and the rostral part of the aqueduct of Sylvius. The fourth ventricle was not outlined and the iter was pushed forward (figure 6a). A chest film revealed peribronchial thickening at the level of the right third and fourth interspaces anteriorly and pleural thickening at the right base (figure 5b).

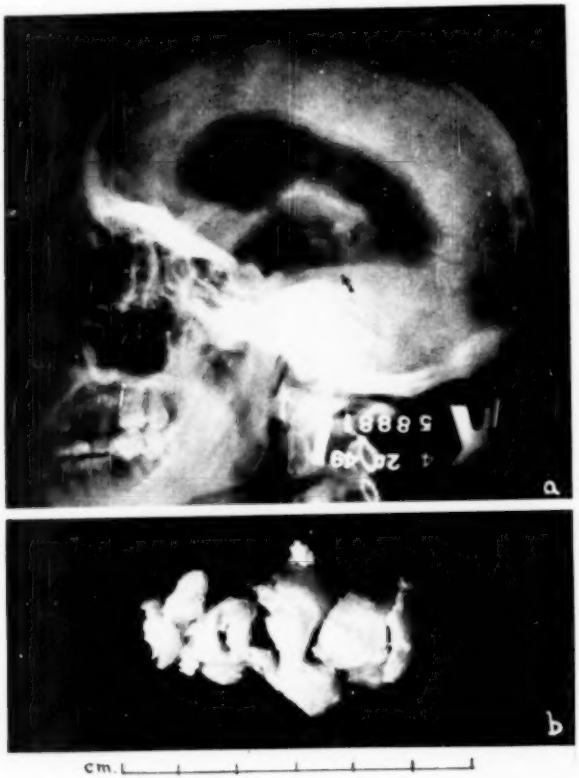

FIG. 6 Case 2. (a) Ventriculogram showing marked dilatation of the ventricular system. Note obstruction of aqueduct; (b) Tuberculoma after removal.

Course in the hospital: The evidence pointed to a rapidly progressive, space-occupying lesion in the posterior fossa, possibly a tuberculoma. On the day following admission, craniotomy was performed. A grayish-yellow, hard, encapsulated mass was found subcortically in the mesiolateral portion of the right cerebellar hemisphere. The mass was fragile and was removed in three portions (figure 6b). Pathologic examination showed it to be a tuberculoma (figure 7).

Streptomycin, 1 gm. daily, was started immediately after operation and continued for ninety days. The drug was also given intrathecally in doses of 50 mg. every two days for fourteen doses.

Immediately following operation, there was considerable improvement in the patient's

condition. Improvement was progressive and all abnormal neurologic findings subsided within one month.

In July 1949, routine films of the lumbar spine revealed lytic involvement of the fourth and fifth vertebrae (figure 8). There were no symptoms attributable to this finding, and he

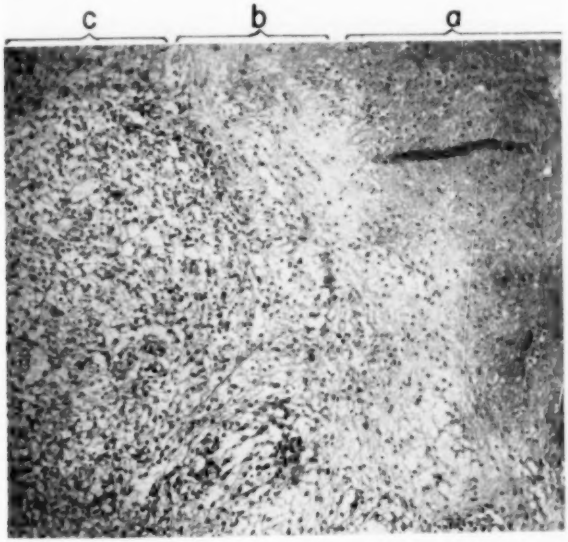

FIG. 7 Case 2. Photomicrograph of section of tuberculoma: (a) Central zone of caseous necrosis; (b) area of cellular infiltration; (c) compressed brain tissue.

FIG. 8 Case 2. Destructive lesion of fourth lumbar vertebra.

was treated conservatively. Roentgenograms of the chest remained unchanged. Examination of specimens of sputum and gastric contents revealed no tubercle bacilli. Parenteral streptomycin therapy was resumed and, in view of the probable development of drug fastness from the streptomycin previously administered, para-aminosalicylic acid therapy was

begun at the same time. His general condition has remained good, although the outcome remains in doubt.

DISCUSSION

It seems that a less pessimistic attitude should be adopted in the approach to clinically manifest tuberculoma of the brain. Even before the newer therapeutic agents became available, the situation was not hopeless. The administration of streptomycin constitutes a measure of protection against the dreaded complication of tuberculous meningitis. Possibilities for the development of bacterial drug-fastness with prolonged use of streptomycin are well known. Because of the difficulty with which streptomycin penetrates encapsulated tuberculous foci in the central nervous system, the bacilli in these areas may remain drug sensitive even after prolonged use of streptomycin has rendered resistant the organisms elsewhere in the body. Tests of sensitivity to streptomycin should be performed whenever possible, as it may be of considerable value to determine the *in vitro* sensitivity of organisms isolated from the patient.

The most effective technique of utilizing streptomycin in connection with surgical removal of intracranial tuberculoma has not been clearly delineated. It is the opinion of some investigators that the drug should be withheld until the actual development of complications. The first patient reported above had received two six-week courses of streptomycin for extracerebral tuberculosis prior to surgery. The possibility existed that the strain of tubercle bacilli in this patient might still be drug sensitive. To safeguard this possibility, it was decided to withold the drug until a time when it might more clearly be needed. Other observers have believed that streptomycin should be administered for a period before and after operation in an attempt to prevent the development of complications. Under these conditions, it would seem reasonable to give the drug both parenterally and intrathecally.

The second patient was critically ill on admission and required immediate surgery for a "tumor" of the brain. At operation, the diagnosis of tuberculoma became apparent and streptomycin therapy was started immediately. This patient had not received the drug previously and thus the tubercle bacilli could be assumed to be sensitive to streptomycin.

In both patients, it was believed that the presence of widespread tuberculosis was not a contraindication to surgery. If the intracranial lesions had not been removed, both patients would almost certainly have died. As it is, these patients are alive eight and thirteen months after operation. Furthermore, with newer developments in the treatment of tuberculosis, the prognosis in previously hopeless disease has been improved. Although the prognosis in both of the patients reported remains guarded, the ultimate outlook is still uncertain and the possibility of arrest of the disease remains.

SUMMARY

Two cases of intracranial tuberculoma, in which the tuberculomas were resected despite the presence of widely disseminated lesions of tuberculosis throughout the body, are described.

The improved prognosis in tuberculosis, including tuberculous meningitis, which stems from use of the newer therapeutic agents, will probably be reflected in improvement of the results following removal of intracranial tuberculoma.

A brief review of the literature on intracranial tuberculoma is presented.

SUMARIO

La Extirpación Cruenta en Presencia de Tuberculosis Generalizada

Descríbense 2 casos en los que estaba indicada la cirugía de urgencia a pesar de haber tuberculosis muy diseminada. Ambos enfermos están vivos todavía, a los ocho y trece meses, respectivamente, de la operación.

Con el advenimiento de los recientes agentes quimioterapéuticos para la tuberculosis se ha iniciado una nueva era en el tratamiento de los tuberculomas cerebrales.

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BOOKS

SEYMOUR M. FARBER, *et al: Cytologic Diagnosis of Lung Cancer. Pp. x–55 with 10 plates in color, Charles C Thomas, Springfield, Illinois, 1950, $6.00.*

This book has been prepared in answer to the great demand for guidance in the application of the cytologic method to the diagnosis of lung cancer. The tremendous interest in this diagnostic procedure which has developed since its revival in recent years has resulted in numerous publications of articles dealing primarily with statistical evaluation of the technique, but to date little morphological description has appeared for the many beginners in cytology. The authors are therefore satisfying, at least in part, the urgent call for authoritative assistance in the preparation of smears, staining, and the recognition of differences between malignant and nonmalignant cells from the respiratory tract.

The chapter on technique describes the methods used to collect sputum, bronchial aspirates, and pleural fluid. Detailed instructions are also given in the treatment of these specimens throughout the several steps involved in fixing, staining, and mounting the smears. The authors use essentially the same technique as that devised by Papanicolaou.

Following a brief discussion of the histologic features of the respiratory tract and the pathologic characteristics of bronchogenic carcinoma, an analysis is made of the technical advantages of the wet smear over the tissue section for the study of cell detail. These include fewer artifacts in the smears (which in sections are due to fixation shrinkage), less cellular deformity from pressure of adjacent cells, and the fact that in smears the cells are seen *in toto*.

The greatest value of the book will be found in its sections pertaining to the identification of nonmalignant as well as malignant cells. The criteria used in determining malignancy are described in detail. The authors correctly emphasize that the separation of the several cytologic criteria for malignancy is artificial since the abnormal features as listed seldom occur singly but are much more frequently found in combination with others. When several abnormal characteristics are found in a single cell or among cells in a group, a positive diagnosis is more easily made.

Basing their results on 1,254 cases which had been followed over long periods of time, the authors found malignant cells either in the sputum or bronchial aspirates in 110 (55 per cent) of 197 patients who were proved by tissue section to have carcinoma of the lung. This represents the sensitivity of the technique in their hands. Both sputum specimens and aspirates were obtained from the same patient in 56 cancer cases, and 36 (64 per cent) were correctly diagnosed as positive. Comparing single sputum specimens with single bronchial aspirates, the percentage of accuracy was approximately the same, namely, 39 per cent and 37 per cent, respectively.

The value of obtaining increased numbers of specimens from a patient is stressed. Whereas 59 per cent of the cases were detected by examination of three

sputum specimens from each, the accuracy rose to 87 per cent when five specimens were obtained. Reporting only two false positives (one due to metaplasia and the other to atypical histiocytes), the authors show a reliability of positive reports which is nearly 100 per cent.

In comparison with bronchoscopic examination, the percentage of positive diagnoses was somewhat better with the cytologic method (55 per cent as against 50 per cent), but the greatest accuracy (92 per cent) resulted when the two methods were combined.

It is emphasized that all diagnostic methods should be utilized to full advantage, but in the absence of confirmatory evidence by endoscopic examination and biopsy, roentgenogram, and so on, it is believed that the cytologic criteria are today sufficiently reliable to justify operation on the basis of positive cytologic evidence alone, *when the reports are made by an adequately trained person.*

A wide assortment of photomicrographs in color are included in ten plates and are helpful, but photographs of cells are never successful in substituting for actual visualization through the microscope.

JOHN F. SEYBOLT

EELCO HUIZINGA AND G. J. SMELT: *Bronchography. Pp. 263 with 150 illustrations, Van Gorcum & Company, Assen-Netherlands, 1949, Cloth.*

This treatise on bronchography is an excellent basic work which has apparently been carefully written after a thrbugh review of the literature and a careful research in anatomy. The authors believe that, with the awakening of interest in the subjects of anatomy, physiology, and pathology of the lungs, there is a definite need for a survey of the subject of bronchography.

This book is a direct outcome of a similar work published in 1927 by Doctor Rap and Doctor Smelt, and was rewritten, modernized and printed in English. The authors, in their associations, seemingly have a wealth of clinical material and considerable experience in this field.

The book contains seven chapters, and the text is well supplemented with illustrations and diagrams. The illustrations, for the most part, are excellent, but like so many European works are printed in the negative rather than in the positive print. This detracts somewhat from the value of the illustrations.

Chapter I deals with the anatomy of the bronchial tree and of the most commonly encountered variations. Chapter II deals with the physiologic variations of the bronchial tree during respiration. A separate chapter was deemed necessary by the authors because these facts have not yet been widely disseminated.

In Chapter III, general considerations of bronchoscopy are included. The importance of knowledge of the anatomy of the bronchial tree is stressed when attempting to obtain a satisfactory segmental filling of the entire bronchial tree. The importance of correlation of bronchographic and bronchoscopic findings in establishing an accurate preoperative diagnosis in lesions of the lung is stressed.

Chapters IV and V describe the anatomy of the lungs as visualized on the bronchogram, and the interpretation of the bronchogram. To students of bron-

chography these chapters have much to offer. The pathologic bronchogram is considered in Chapter VI. Discussion is grouped into three categories: (*1*) dilatation and the formation of cavities in lungs; (*2*) stenosis and obstruction; (*3*) displacements. The illustrations and discussions in this chapter are certainly worth while in establishing clearer thinking for the average student of bronchography.

In Chapter VII the authors describe their technique of segmental filling of the entire bronchial tree by nasal drip. Again, the importance of the knowledge of anatomy of the bronchial tree is stressed. The authors make no claim that their technique for filling the bronchial tree is superior to other accepted methods, but merely state that their method has been extremely satisfactory. The importance of correct positioning during filling of the various segments is stressed.

This book seems to fill a definite need for a basic treatise on the subject of bronchography. Its historical approach, as well as its anatomic and physiologic approach, leaves little to be desired in a book which serves well as a basic text for the student of bronchography.

ROBERT W. BYRNE

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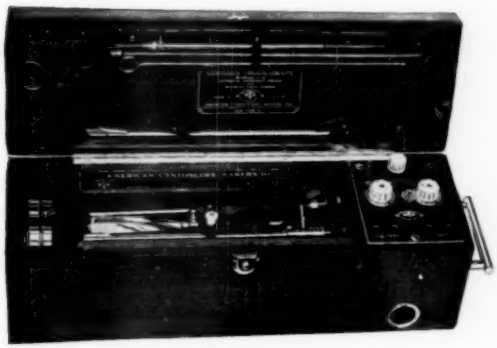

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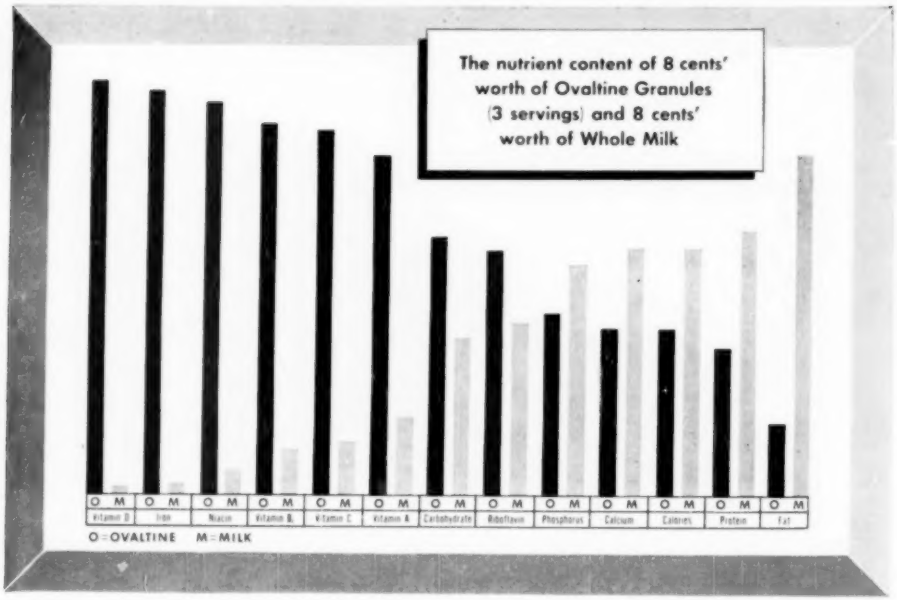

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THE AMERICAN REVIEW OF TUBERCULOSIS
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NATIONAL TUBERCULOSIS ASSOCIATION

Annual Meeting **May 15–18, 1951**

Cincinnati, Ohio

The annual meeting of the National Tuberculosis Association will be held in Cincinnati, Ohio, May 15–18, 1951. The Netherland Plaza Hotel will be headquarters.

Some 1500 rooms have been promised by the hotels listed below for the accommodation of those attending the meeting. Arrange to share a double room if possible.

Application for room reservations should be made directly with the hotel of your choice.

Hotel	*Address*	*Single*	*Double*
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*Ref.: 1. *V. A. 9th Streptomycin Conference, April 1950*
2. *Carstensen, B.: PAS in Tuberculosis, Amer. Rev. Tuberc. 1950, 61: 613*

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